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Accutane: Post-Approval Drug Regulation in a Risk Management Framework

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Abstract*¹

The acne drug Accutane lies at the center of a movement to expand post-approval controls on drug regulation in an effort to effectively manage drug risks. Accutane's regulatory history tracks a trend towards the increasing emphasis in drug regulatory policy on post-marketing risk management. The Accutane experience illustrates the fundamental regulatory problems of drug safety, drug availability and individual autonomy driving this shift. Recent reform of Accutane regulation through the S.M.A.R.T. program both exemplifies the trend and suggests its limitations.

I. Introduction

“As an individual practitioner, it was my decision that this patient be treated with Accutane, and it should remain my decision and not that of the manufacturer the pharmacist, or anyone else.”²

¹* I would like to thank Mr. Peter Barton Hutt for his encouragement and advice during the preparation of this paper.

“The FDA has to regulate drugs in the real world. In this world doctors are imperfect. . . People are not always straightforward about their sexual activity. Women with acne come into offices demanding treatment. . . One of the world’s most potent teratogens cannot be left to ride on all these waves of chance.”³

This paper explores the story of Accutane, or Isotretinoin, a drug approved in 1982 for the treatment of severe recalcitrant cystic acne.⁴ Its regulatory history, and the debate captured by the quotations above, tracks the larger story of American drug regulatory policy and its increasing emphasis on post-approval drug regulation.

Accutane’s story is inextricably intertwined with that of another drug—thalidomide. Thalidomide was widely used in Europe in the 1960s as a morning sickness remedy and a sleeping pill.⁵ However, much like Accutane, the drug also caused severe deformities in thousands of babies.⁶ In the United States, Thalidomide was distributed to doctors for purposes of investigation, but it was never mass marketed. A Food and Drug Administration (“FDA”) medical officer, Dr. Frances O. Kelsey, had rejected the drug for non-compliance with the safety requirements of the Federal Food Drug and Cosmetic Act of 1938 (“1938 Act”).⁷

The 1938 Act was passed in the wake of an earlier drug-related tragedy; In 1937, “Elixir Sulfonilamide” killed at least 70 people when it was widely marketed with neither animal nor human safety testing.⁸ The tragedy placed into sharp relief the inadequacies of the then prevailing regulatory system structured by the Food and Drug Act of 1906 (“1906 Act”).⁹ The 1906 Act required that drugs purity and strength standards to prevent misbranding and adulteration.¹⁰ Yet it provided no safety or efficacy standards and prosecution under the Act was virtually impossible.¹¹ The Act offered no preventive remedies, but provided manufacturers

⁴Joan H. Krause, *Accutane: Has Drug Regulation in the United States Reached its Limits?*, 6 J.L. AND HEALTH 7 (1991-92)

⁵*Id.* at 4

⁶*Id.*

⁷*Id.*

⁸HUTT, PETER BARTON & RICHARD A. MERRILL, *FOOD AND DRUG LAW* 476 (1991)

⁹Krause, *supra* note 3, at 4.

¹⁰*Id.*

¹¹*Id.*

numerous loopholes.¹² In addition, its interpretation in the courts substantially limited its effectiveness.¹³ To remedy the situation, Congress passed the 1938 Act.¹⁴ In accordance with its provisions, manufacturers must provide evidence of their drug's safety.¹⁵ The 1938 Act also made prosecution more feasible by eliminating the 1906 Act's intent requirement in misbranding cases.¹⁶ Factory inspections were authorized as a preventative measure under the Act, injunctive relief became available and cosmetics and food were brought under federal regulation.¹⁷ Nevertheless, proof of a drug's effectiveness was still not required under the 1938 Act.¹⁸

The Thalidomide tragedy prompted Congressional amendments.¹⁹ In 1962, Congress required by a unanimous vote that products meet both safety and efficacy standards.²⁰ The Amendments established detailed drug approval procedures, including the animal and human clinical trials performed today.²¹

Twenty years later, with this system largely intact, the United States became the first country to approve Accutane for the treatment of severe recalcitrant acne.²² Like Thalidomide, Accutane causes debilitating birth defects.²³ Even minimal exposure to during pregnancy produces at least a 25 percent chance of having a baby with severe birth defects.²⁴ Such problems include mental retardation, lethal heart defects, and malformed faces lacking ears or featuring ears below the chins.²⁵ An additional 40 percent of fetuses are spontaneously aborted.²⁶

¹² *Id.*

¹³ *Id.*

¹⁴ *Id.* at 4-5

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ *Id.*

²¹ *Id.*

²² *Id.* at 7

²³ Gina Kolata, Europeans Place Stiffer Curbs on Acne Drugs, N.Y. TIMES, Apr. 28, 1988, at A1.

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.*

The severity of these teratogenic risks are frequently compared to those of Thalidomide, which often produced babies of normal intelligence, but with flipper like limbs.²⁷ Yet in Accutane's case, it was the U.S. rather than Europe that first approved the drug for mass marketing.²⁸ Once approved in Europe, Accutane was usually subjected to far stricter restrictions on its distribution.²⁹ England and Spain carefully monitored Accutane patients and limited prescribing power to selected specialists.³⁰ In Britain, a woman needed to first visit her own doctor and receive a referral to one of these dermatologists.³¹ She would only receive the drug after receiving warnings, signing an informed consent form, and agree to abort any pregnancy conceived during therapy.³² The United States generally rejected strict post-marketing regulation while emphasizing pre-approval safety testing.³³

Yet during the 1980s, critics of FDA often portrayed American drug regulatory policy as overly cautious; exacting pre-approval investigation seemed to deprive Americans of valuable drugs available overseas.³⁴ Accutane's relatively rapid approval and unrestricted post-marketing distribution conflicted with the critics' image of FDA's "drug lag."³⁵ However, Accutane's prompt release was perhaps a harbinger of the speedier drug approval schemes produced by subsequent revisions of regulatory policy in the 1990s; the Prescription Drug User Fee Act of 1992 ("PDUFA") and the Food and Drug Modernization Act of 1997 have since accelerated access to new drugs.³⁶

Today Accutane lies at the center of a backlash against this accelerated process. Recent revisions of Accutane regulation through the System to Manage Accutane Related Teratogenicity, ("S.M.A.R.T"), reflect worries

²⁷ *Id.*

²⁸ *Id.*

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.*

³² *Id.*

³³ See Harvey Teff, *Drug Approval in England and the United States*, AM. J. COMP. L. 567, 579 (1985).

³⁴ Kolata, *supra* note 22

³⁵ *Id.*

³⁶ See Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, CATH. U. L. REV. 449, 462 (2000)

that faster review and relatively lax post-marketing controls endanger society.³⁷ Allegations that Accutane may also cause depression and suicide have only intensified these concerns.³⁸

In Part II of this paper, I examine the recent debate over FDA risk management strategies and analyze a general shift in American drug regulatory policy towards post-marketing controls. In Part III, I trace the regulatory history of Accutane, from its rapid approval in 1982 to the S.M.A.R.T program’s imposition of stricter post-marketing regulation in 2002. Although Accutane did not instantly prompt the sudden sweeping reform sparked by Thalidomide, its unique regulatory history departs dramatically from traditional drug regulation.

Reasons for this departure lie in the core tensions at work in American drug regulation policy. Part IV explores the role that fundamental regulatory dilemmas have played in Accutane’s story. A tradeoff between safety and availability often underlie regulatory decisions. For Accutane, post-marketing controls may ensure fewer pregnancy exposures and adverse psychiatric events. Yet they also threaten to limit the drug’s availability and to fuel a dangerously unregulated underground market. Also shaping the Accutane debate have been competing conceptions of acne and birth defects. At one extreme, the debate risks trivializing acne as a uniformly superficial annoyance, rather than recognizing its potentially devastating social and emotional consequences. At the other extreme, it risks minimizing the suffering of those born with Accutane-related birth defects. Ironically, the very severity of their disabilities may make Accutane’s victims “too easily hidden from public view” and their problems too easily overlooked.³⁹ Unlike Thalidomide victims, Accutane

³⁷See Diane Knich, *New Restrictions on Acne Drug Aim to Curb Birth Defects*, BOS. GLOBE, Apr. 11, 2002.

³⁸See generally Accutane—*Is this Acne Drug Treatment Linked to Depression and Suicide?: Before the House Committee on Government Reform*, 106th Congress (2000) [hereinafter *House Hearings*]; See also Katherine Hobson, *Mind versus Face*, U.S. NEWS & WORLD REPORT, Apr. 1, 2002.

³⁹See Krause supra note 3 at 28.

victims are usually so disabled that they cannot testify to the hardships they face.⁴⁰ Issues of individual choice, maternal responsibility and physician autonomy further complicate the debate as Accutane regulation struggles to balance the welfare of the unborn fetus with the freedom of patients and doctors.⁴¹

The Accutane experience reflects broader risk management dilemmas. In Part I, I explore a significant shift in American drug regulatory philosophy exemplified by the Accutane experience.

II. Overview of FDA Risk Management Policy

A. Introduction to the Task Force on Risk Management

By May 1999, growing criticism of FDA prompted FDA Commissioner Dr. Jane Henney to commission a Task Force on Risk Management.⁴² The Task Force responded to critics with a report entitled *Managing the Risks from Medical Product Use—Creating a Risks Management Framework*.⁴³ Critics had alleged that speedier review of New Drug Applications (“NDAs”) had resulted in more unexpected adverse drug reactions (“ADRs”).⁴⁴ They also suggested that FDA’s post-approval surveillance mechanisms inadequately monitored these ADRs.⁴⁵ These charges contrasted sharply with critics’ longstanding concerns about FDA alleged “drug lag.”⁴⁶ In the 1980s and early 1990s, critics considered the approval process too lengthy and the delay

⁴⁰ See *id.*

⁴¹ See *id.*, at 28.

⁴² Managing the Risks From Medical Product Use—Creating a Risk Management Framework: Report to the FDA Commissioner from the Task Force on Risk Management 17 (May 1999), available at <http://www.fda.gov/oc/tfrm/riskmanagement.pdf> (last visited Apr. 28, 2002) [hereinafter *Report*]

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ See Denise Grady, *Need is Seen for a Drug Safety Board*, N.Y. TIMES, Dec. 29, 1998, at F7; Gina Kolata, *The F.D.A. Approves a Drug. Then What?*, N.Y. TIMES, Oct. 7, 1997 at F1.

⁴⁶ See Report, *supra* note 41, at 16.

with which AIDS and cancer patients received new therapies too extensive.⁴⁷ Yet by the late 1990s there were calls for the retrenchment of expedited review procedures.⁴⁸

B. Overview of Traditional Drug Approval Process

Traditionally, FDA has required that manufacturers seeking new drug approval test their product in laboratory animals.⁴⁹ Animal testing reveals information on the drug's toxicity, its absorption in the body and safe dosage.⁵⁰ After completion of animal testing, the drug's sponsor submits its research to FDA and proposes testing on human subjects.⁵¹ This proposal describes the contemplated research in the form of an "investigational new drug application" or IND.⁵² Controlled testing in humans can only begin once FDA determines that such testing can safely be conducted with human volunteers.⁵³

If FDA makes such a determination, then the drug's sponsor may commence human trials.⁵⁴ These tests usually contain three phases.⁵⁵ Phase I focuses on the drug's safety.⁵⁶ Over several months, fewer than 100 healthy, paid volunteers usually take the drug to determine its safety.⁵⁷ Phase II trials begin if the drug passes the Phase I tests.⁵⁸ In Phase II, researchers examine the drug's effectiveness in treating the ailments it is designed to combat.⁵⁹ Several hundred patients with the particular disease that the drug targets are

⁴⁷*Id.*

⁴⁸Grady, *supra* note 44

⁴⁹*See* Krause, *supra* note 3, at 5.

⁵⁰*Id.*

⁵¹*Id.*

⁵²*Id.*

⁵³*Id.*

⁵⁴*Id.*

⁵⁵*Id.*

⁵⁶*Id.*

⁵⁷*Id.*

⁵⁸*Id.*

⁵⁹*Id.*

usually involved.⁶⁰ Phase II studies usually last for several months to two years and are randomized control trials; a “treatment” group receives the drug while a control group receiving either a placebo or the standard treatment is established for comparison.⁶¹ In “blinded” Phase II studies, the patient’s group is concealed from both the patient and the doctor delivering the drug.⁶² Finally, Phase III approximates normal medical usage of the drug; several thousand patients with the particular condition may take the drug in an attempt to reveal a drug’s rarer side affects.⁶³

Phase III may last for four years or more.⁶⁴ The sponsor files a “New Drug Application,” or NDA, with FDA upon completion of Phase III. FDA’s approval of the drug hinges on proof of its safety and the development of appropriate labeling for the drug.⁶⁵ Labels must state the drug’s approved indications, its recommended dosage, contraindications, side effects and warnings.⁶⁶ This information usually appears on “package inserts” accompanying the drug.⁶⁷ Sometimes, however, patients and doctors receive labels developed especially for their respective needs.⁶⁸

In particular cases, patients had received investigational new drugs, (“INDs) after FDA had issued ad hoc “Treatment INDs” or “Compassionate INDs.” In 1987, the FDA’s official IND policy was revised so that patients with immediately life-threatening illnesses could receive experimental drugs without enrolling in a research trial.⁶⁹ Under the revised policy, drugs for immediately life-threatening diseases could receive approval after Phase II trials.⁷⁰ Similarly, drugs for serious illnesses could receive approval during Phase III.⁷¹ In 1988 FDA, further increased the availability of new drugs by proposing a “fast-track” approval

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Id.*

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ *Id.*

⁷¹ *Id.*

program for drugs treating life-threatening or severely debilitating illnesses.⁷² This program provided for more lenient FDA risk-benefit analysis of the drugs and entailed greater collaboration between FDA and the sponsor in developing Phase II clinical trials.⁷³

In 1992, steps to accelerate access to new drugs continued. FDA regulations relaxed scientific evidence requirements for drugs used to treat serious or life-threatening illnesses “that provide meaningful therapeutic benefit patients over existing treatment.”⁷⁴ To qualify for expedited review under this regulation, sponsors must conduct post-approval studies of the drug.⁷⁵ Congressional passage of the Prescription Drug User Fee Act of 1992 (PDUFA) also accelerated the process.⁷⁶ Pursuant to PDUFA the sponsors of new drug and biological products provide FDA with user fees to support the review of new pharmacological products.⁷⁷ The Food and Drug Modernization Act of 1997 (FDAMA) reauthorized PDUFA and relaxed the “substantial evidence” standard so that NDA sponsors need only submit one rather two controlled clinical trials.⁷⁸

C. Criticism of Expedited Review

Critics of FDA questioned the wisdom of the resulting expedited review.⁷⁹ A prominent opponent of the reforms was Public Citizen’s Health Research Group, directed by Dr. Sidney Wolfe and founded by consumer advocate Ralph Nader in 1971.⁸⁰ In a press conference, the advocacy group reported the results of its anonymous survey of FDA medical officers, agency employees assigned to oversee drug evaluations.⁸¹

⁷² *Id.*

⁷³ *Id.* at 6

⁷⁴ See Noah, *supra* note 35, at 462-463

⁷⁵ See *id.*

⁷⁶ See Report, *supra* note 41, at 17.

⁷⁷ See *id.*

⁷⁸ See *id.* at 16

⁷⁹ See Denise Grady, *In a Survey, the F.D.A. is Accused of Hasty Approval of Drugs*, N.Y. TIMES, Dec. 3, 1998, at A1.

⁸⁰ See *id.*

⁸¹ See *id.*

Nineteen medical officers stated that 27 drugs were approved over their objections, seventeen considered FDA's safety and efficiency standards lower than they had been in the past and nineteen reported feeling more pressured by Congress, the pharmaceutical industry and FDA to approve drugs for mass marketing.⁸² Public Citizen alleged that pressures to accelerate drug approval had threatened public safety.⁸³ Complaints had intensified as several FDA approved drugs were withdrawn from the market upon discovery of previously unforeseen side effects or dangerous interaction with other drugs.⁸⁴ Among these drugs were the diet drug Redux, the high blood pressure medication Posicor, and the allergy drug Seldane.⁸⁵ Drs. Raymond Woosley, Alastair J.J. Wood and Michael Stein have likened these drug recalls to airplane crashes.⁸⁶ Writing in the *New England Journal of Medicine*, they called for the establishment of an independent safety review board to investigate drug 'crashes' much as the transportation board investigates plane crashes.⁸⁷ The Doctors contended that if the same organization that approves plane manufacturers and airlines should not investigate disasters involving those planes and manufacturers, then the same entity that approves drugs should not be the sole investigator of the drug's post-approval reactions.⁸⁸ The doctors noted that since accelerating its approval process FDA had approved drugs at almost twice its previous rate.⁸⁹ For them, this acceleration strains an inherently limited drug regulatory system; pre-approval clinical investigators, of relatively short duration and involving a relatively small number of subjects from a relatively narrow sample of subjects, may not reveal all drug risks.⁹⁰ The doctors also deemed FDA's post-approval surveillance mechanisms too informal to promptly detect these risks and are feared that the already impaired system would suffer further strain as more drugs enter the market annually.⁹¹ Post-marketing, drugs become

⁸²See *id.*

⁸³See Report, *supra* note 41, at 17.

⁸⁴See Noah, *supra* note 35, at 491

⁸⁵See *id.*, at 491; See Grady; *supra* note 44.

⁸⁶Grady, *supra* note 44.

⁸⁷See *id.*

⁸⁸See *id.*

⁸⁹See *id.*

⁹⁰See *id.*; see also Noah, *supra* note 35, at 458-462.

⁹¹See Grady, *supra* note 44.

widely available to a diverse set of patients who may take the drug in combination with other prescriptions.⁹² Thus, some adverse reactions may first surface outside of this controlled environment.⁹³ Dr. Woosley characterized these post-approval patients as unwitting subjects in a massive experiment and argued that such an experiment needs more careful monitoring.⁹⁴

Holders of an NDA are required by the Food Drug and Cosmetic Act to report any data relating to clinical experiences with drug.⁹⁵ However, FDA regulations do not require holders of an approved NDA to actively seek such information.⁹⁶ When a health care professional or consumer spontaneously reports an adverse reaction, the manufacturer must submit an adverse experience report.⁹⁷ Noah argues that this “‘mandatory’ system is only as effective as the degree of voluntary participation permit.”⁹⁸

Although health care providers are not legally mandated to report adverse drug reactions, they are ethically obliged to do so.⁹⁹ In its first concerted effort to formally involve physicians in post-marketing surveillance, FDA established the MedWatch system in 1993.¹⁰⁰ Physicians receive one page forms and are asked to complete them in order to report all serious adverse reactions.¹⁰¹ Included in the events physicians are asked to report are death, disability, birth defects and miscarriage.¹⁰²

Barbara A. Noah considers the quality and effectiveness of physician participation in the program “moderately favorable.”¹⁰³ Nevertheless, she notes that while the quality of the reports has improved, the overall number of reports has declined since the MedWatch launch. Spontaneous reporting of ADRs peaks at the end of a second year of the drug’s marketing, but declines dramatically thereafter, regardless of presumably

⁹²See *id.*

⁹³See *id.*

⁹⁴See *id.*

⁹⁵See Noah, *supra* note 35, at 466.

⁹⁶See *id.*

⁹⁷See *id.*, at 469.

⁹⁸See *id.*

⁹⁹See *id.*, at 477.

¹⁰⁰See *id.* at 478.

¹⁰¹See *id.*

¹⁰²See *id.*

¹⁰³See *id.*

constant rates of prescriptions and ADRs.¹⁰⁴

Noah suggests, that increasingly common managed care organizations may foster the routine collection and reporting of ADRs because they can gather and analyze masses of data.¹⁰⁵ Yet other features of managed care plans may offset this advantage.¹⁰⁶ Patients change physicians far more often under managed care, impeding communication with doctors.¹⁰⁷ Communication is also hampered by pressure to reduce the duration of each patient visit.¹⁰⁸ As lines of communication erode, the risks to monitor multiply; under managed care doctors prescribe more pharmaceuticals to manage chronic disease.¹⁰⁹

Indeed, by one 1998 report, only a fraction of doctors can even recognize the forms FDA provides to report adverse events.¹¹⁰ Doctors and other health care workers may often be unaware that they are expected to detect and report serious medication side affects.¹¹¹ Thus some doctors and scientists have called for more formal, possibly mandatory, involvement of health care workers in the surveillance process.¹¹²

D. The Task Force Defense of Pre-Approval Procedures

The Task Force's Report acknowledged the growing complexity of the health care environment and proposed changes to meet its demands.¹¹³ Healthcare is no longer "provided by a family practitioner who treated patients from cradle to grave," the Report notes.¹¹⁴ The Report reflects a growing emphasis on post-marketing

¹⁰⁴ See *id.*

¹⁰⁵ See *id.*, at 480.

¹⁰⁶ See *id.* at 479

¹⁰⁷ See *id.* at 479-480.

¹⁰⁸ See *id.* at 479.

¹⁰⁹ See *id.* at 479.

¹¹⁰ See Kolata, *supra* note 44.

¹¹¹ See *id.*

¹¹² See *id.*

¹¹³ See *generally*, Report, *supra* note 41, at 20.

¹¹⁴ See *id.*

risk management strategies, a trend away from disproportionate reliance on pre-approval testing.¹¹⁵

Nevertheless, the Task Force defended the quality of FDA's pre-market approval process.¹¹⁶ FDA's data showed no increase in the rate of drug withdrawals since PDUFA. It also found no evidence that drugs approved since PDUFA caused higher rates of serious adverse events on the market.¹¹⁷ Rates of serious adverse events identified post-marketing were lower for drugs approved under PDUFA.¹¹⁸ The Task Force also criticized Public Citizen's survey method; the group failed to collect information on how frequently or when medical officers' recommendations to disapprove a product were not followed—facts relevant in assessing the true extent of the problems they alleged.¹¹⁹

Yet the Task Force recommended improvements to FDA's quality control system, including periodic review of a sample of product approval administrative records, procedures for the continuation of review despite administrative disruptions and evaluation of whether scientific disputes among reviewers predicts post-marketing problems.¹²⁰ The Task Force also recommended ongoing professional education and core competency training for reviewers, the completion and updating of Good Review Practice ("GRP") documents and the analysis of and incorporation into GRP documents of post-marketing events.¹²¹ Additionally, the task force proposed possible expansion of community based trial centers and the concentration of early post-approval use in certain populations for whom new product would be especially advantageous.¹²² Overall however, the task force found that the key elements of FDA's quality control system were intact.¹²³

¹¹⁵See generally Report, *supra* note 41, at 63-70.

¹¹⁶See *id.* at 35-42.

¹¹⁷See *id.* at 35.

¹¹⁸See *id.*

¹¹⁹See *id.* at 18.

¹²⁰See *id.* at 49-50.

¹²¹See *id.*

¹²²See *id.*

¹²³See *id.*

E. Post-Marketing Surveillance Reform

The Report acknowledged the need for greater reform of FDA’s post-marketing surveillance¹²⁴. The Task Force noted the increasingly challenging environment in which post-marketing monitoring occurs, painting a portrait of the current health care climate similar to that of FDA’s critics.¹²⁵ This account included frequent doctor changes, shorter patient visits and the pressure to prescribe items approved by managed care plans.¹²⁶ Yet unlike its critics, the Report shifted emphasis from the post-market monitoring of *unexpected* adverse reactions, to surveillance of *expected* adverse reactions.¹²⁷ Many of the most highly publicized drug withdrawals involved the product’s unanticipated side effects.¹²⁸ Seldane and Redux, for example, were withdrawn from the market upon discovery of unforeseen drug interactions and side effects respectively.¹²⁹ FDA, however, reported that its post-marketing monitoring system was performing to accomplish the purposes for which it was designed—“to detect adverse events not previously observed.”¹³⁰ Nevertheless Dr. Jane Henney has stressed that most injuries and deaths caused by medical products result from their *expected* results.¹³¹ For example, Accutane’s risk of birth defects are well known; post-marketing monitoring of Accutane would monitor the extent of a known problem.

The Report suggests that FDA could assume a more proactive risk management role post-marketing, departing from its traditionally passive post-marketing activity.¹³² It reports, “[t]he management of risks associated with using medical products, known as the practice of medicine, has traditionally been left in the hands of

¹²⁴ See *id.* at 52.

¹²⁵ See *id.* at 51.

¹²⁶ See *id.* at 53.

¹²⁷ See *id.* at 51.

¹²⁸ See Noah, *supra* note 35, at 486, 492.

¹²⁹ See *id.*

¹³⁰ See Report, *supra* note 41, at 52.

¹³¹ Jane E. Henney, M.D., Remarks of the Commissioner of Food and Drugs, 55 FOOD DRUG L.J. 1, 1 (2000); See Report, *supra* note 41, at 12.

¹³² See Report, *supra* note 41, at 92.

health professionals.”¹³³ Although the Report acknowledges that the medical community has resisted FDA’s restrictions on its practices, it argues that the medical community has increasingly accepted post-approval FDA regulation.¹³⁴ Among the possible reforms, the Report suggests that FDA could impose restrictions on product distributions, impose safety programs for risky products—including mandatory education programs for prescribers and patients, mandatory re-labeling or re-approval of products—and restrict drugs to certain uses or prescriber categories.¹³⁵ The Report noted that such efforts would be particularly appropriate for drugs with especially high risks.¹³⁶

The Report also suggested improvement to FDA’s risk communication strategies.¹³⁷ Although FDA is already actively engaged in the risk communication process, the Report suggests that these activities would be more successful within a systematic strategy.¹³⁸ For example, FDA could categorize the types and severity of risks and base their communication strategy on these classifications.¹³⁹ The Report proposed a Government sponsored database that health care professionals could access.¹⁴⁰ As an example of the information suitable for such a database, the Report lists “registry information on the outcomes of the use of drugs during pregnancy.”¹⁴¹

F. A Comparative Perspective

¹³³ *See id.*

¹³⁴ *See id.*

¹³⁵ *See generally Id.* at 92-94.

¹³⁶ *See id.* at 92.

¹³⁷ *See id.* at 93-96.

¹³⁸ *See id.* at 93.

¹³⁹ *See id.*

¹⁴⁰ *See id.*

¹⁴¹ *See id.* at 94.

These proposals reflect a shift in U.S. regulatory philosophy towards the British model.¹⁴² Harvey Teff, in his comparative study of drug approval in England and in the United States, characterizes U.S. and British regulatory philosophy as fundamentally different.¹⁴³ According to Teff, the U.S. drug approval process places more emphasis on ensuring drug safety prior to the product's marketing than does its British counterpart.¹⁴⁴ By contrast, the British system has traditionally stressed post-marketing risk management strategies.¹⁴⁵

In part, Teff attributes this difference to British regulators' more explicit acknowledgement "of the unpalatable truth that the research process continues even after a license drug has been made available for general prescription."¹⁴⁶ Even with demanding pre-marketing testing, rare side effects will often only appear once a far greater portion of the population uses the drug post-approval.¹⁴⁷ In the U.K., it is far more common for certain drugs only to be prescribed by hospitals or by certain medical specialists¹⁴⁸. Accutane is subject to such limitations in the U.K.¹⁴⁹ There has also been far more attention paid to the post-marketing monitoring of adverse events in the U.K. than in the U.S.¹⁵⁰ By contrast, FDA begins its supervision of the drug's testing earlier in the regulatory process.¹⁵¹

Underlying these different approaches are the political and social climates in which American and British regulators work.¹⁵² Britain is relatively small, has a more homogenous population and has a national

¹⁴² See Teff, *supra* note 32, at 579.

¹⁴³ See *id.*

¹⁴⁴ See *id.*

¹⁴⁵ See *id.*

¹⁴⁶ See *id.*

¹⁴⁷ See *id.*

¹⁴⁸ See *id.*

¹⁴⁹ See Kolata, *supra* note 22; See also 1988 Hearing, *supra* note 2, at 139 (testimony of Dr. Lynn Silver)

¹⁵⁰ See Teff, *supra* note 32, at 579.

¹⁵¹ See *id.*

¹⁵² See *id.*

health care system equipped to gather and study masses of data.¹⁵³ These factors make more feasible post-marketing controls and monitoring.¹⁵⁴ In addition, Teff argues that the American political system demands more formal accountability of its regulators; Congressional oversight, media scrutiny and an active consumer lobby pressure FDA to achieve maximum safety prior to mass marketing.¹⁵⁵ In the U.K., a tradition of administrative secrecy has relieved some of this pressure.¹⁵⁶

G. FDA Sub-Committee on Drug Safety and Management

The Task Force Report suggests a departure from tradition.¹⁵⁷ The Report's call for enhanced post-marketing surveillance, proposals of patient registries and limitations on prescribing power echo the British post-marketing approach.¹⁵⁸ The same Congressional scrutiny, media attention and consumer lobbying that had pressured FDA to perform extensive pre-approval investigation now demands strengthening of post-marketing supervision.¹⁵⁹

This shift is reflected institutionally in the establishment of FDA's new Subcommittee on Drug Safety and Risk Management, a group expected to gain full committee status.¹⁶⁰ The group will focus on the safety

¹⁵³ See *id.*.

¹⁵⁴ See *id.*.

¹⁵⁵ See *id.* at 579-580

¹⁵⁶ See *id.*.

¹⁵⁷ See Report, *supra* note 41, at 92.

¹⁵⁸ See *id.*.

¹⁵⁹ See *id.*.

¹⁶⁰ See Francesca Lunzer Kritz, *FDA to Weigh New Controls on Problematic Drugs; Lotronex Will Be First for Consideration by New Panel*, WASH. POST., Apr. 16, 2002 at F01.

issues of approved drugs.¹⁶¹ In discussing the sub-committee, reporter Francesca Lunzer Kritz asks a question steeped in the traditional philosophy demanding exacting pre-approval scrutiny, “Why not just get all the kinks out before approving a drug?”¹⁶² She answers her own question with acknowledgement of the reality of drug regulation, “Often all the kinks aren’t known then... often rare side effects don’t show up until a drug is being used in hundreds of thousands of people.”¹⁶³ Among the sub-committee’s concerns will be demands that already approved drugs be banned from the market.¹⁶⁴ Other risk management missions of the group are suggested by the experiences of its members.¹⁶⁵ Members include the Director for the Institute for Safe Medication Practices, a nonprofit organization concentrating on medication errors, and a psychologist who has studied risk communication via patient package inserts.¹⁶⁶ At its most recent meeting, the sub-committee considered re-introducing the irritable bowel syndrome drug, Lotronex, despite its side affect of ischemic colitis.¹⁶⁷ Two more meetings are scheduled for this year.¹⁶⁸

Accutane regulation illustrates the ideological shift underlying the sub-committee’s establishment. Part III traces the drug’s regulatory history with its increasing emphasis on strengthening post-marketing Accutane controls.

III. History of Accutane Regulation

A. Acne

¹⁶¹ *See id.*

¹⁶² *See id.*

¹⁶³ *See id.*

¹⁶⁴ *See id.*

¹⁶⁵ *See id.*

¹⁶⁶ *See id.*

¹⁶⁷ *See id.*

¹⁶⁸ *See id.*

Accutane is prescribed to combat acne.¹⁶⁹ The basic cause of acne is unknown, but scientists know that it is a disease of the pilosebaceous units.¹⁷⁰ These consist of oil glands connected to hair follicles.¹⁷¹ In acne patients, the lining of the hair follicle changes to prevent sebum, the oily substance produced by the sebaceous gland, from passing through the follicle to the skin's surface.¹⁷² In normal patients, the sebum empties onto the skin's surface through the follicle.¹⁷³ By contrast, the cells lining the acne patient's follicle shed too quickly and clump together to block the follicle's opening.¹⁷⁴ As the sebum remains trapped in the skin, bacteria that normally live harmlessly on the skin grows in the hair follicle and produce inflammation causing chemicals.¹⁷⁵ The pilosebaceous units are most common on the areas of the body on which acne is most likely to appear—the face, scalp upper back and chest.¹⁷⁶

Acne is generally classified by the kinds of lesions on the patient's body.¹⁷⁷ Often, however, doctors can debate the appropriate classification of a condition.¹⁷⁸ Patients may suffer from different kind of lesions simultaneously.¹⁷⁹ Accutane was originally indicated for severe cystic acne, a disease that results in large, painful and scarring lesions.¹⁸⁰ Defining cystic acne has been an important issue in determining the appropriate use of Accutane.¹⁸¹

¹⁶⁹See *House Hearings*, supra note 37, (statement of Dr. David Pariser, Chief of Dermatology and Professor of Dermatology at the Eastern Virginia Medical School at Norfolk.)

¹⁷⁰See *id.*

¹⁷¹See *id.*

¹⁷²See *id.*

¹⁷³See *id.*

¹⁷⁴See *id.*

¹⁷⁵See *id.*

¹⁷⁶See *id.*

¹⁷⁷*Id.*

¹⁷⁸See *1988 Hearings*, supra note 2, at 112.

¹⁷⁹See *House Hearings*, supra note 37, (statement of Dr. David M. Pariser)

¹⁸⁰See *1988 Hearings*, supra note 2, at 24. (statement of Dr. David Graham, Group Leader, Epidemiology Branch, Office of Epidemiology and Biostatistics.)

¹⁸¹See *id.*

B. Acne Treatments

The first step doctors usually recommend for acne treatment is gentle cleansing of the skin.¹⁸² According to the American Academy of Dermatology, the skin should be washed twice daily with water and a mild cleanser.¹⁸³ This reduces excess oils on the skin's surface.¹⁸⁴ Yet washing is rarely a sufficient remedy and medication is normally required.¹⁸⁵ Most patients start by applying an over-the-counter gel, cream or lotions several times a day.¹⁸⁶ Topical treatments often contain either benzoyl peroxide, salicylic acid, sulfur or resorcinol.¹⁸⁷ These popular treatments prevent follicles from plugging. Benzoyl peroxide-containing products can also inhibit bacterial overgrowth.¹⁸⁸ Yet many patients also require prescription medications.¹⁸⁹ Doctors prescribe antibiotics in either pill or topical form to stop or slow the growth of bacteria.¹⁹⁰ In addition, drugs called retinoids, of which Accutane is an example, combat acne by unplugging blocked follicles or reducing the amount of sebum produced.¹⁹¹

C. Accutane

Accutane is an oral retinoid, also known as isotretinoin.¹⁹² The drug is a Vitamin A derivative.¹⁹³ By

¹⁸²Drs. Jonathan Fielding and Valerie Ulene, *Our Health: Many Therapies Hit the Spot for Relief of Acne*, L.A. TIMES, March 25, 2002, at S7

¹⁸³*See id.*

¹⁸⁴*See id.*

¹⁸⁵*See id.*

¹⁸⁶*See id.*

¹⁸⁷*See id.*

¹⁸⁸*See id.*

¹⁸⁹*See id.*

¹⁹⁰*See id.*

¹⁹¹*See id.*

¹⁹²*See House Hearings*, supra note 37, (statement of Dr. James O'Donnell, Assistant Professor of Pharmacology at the Rush Medical College.)

¹⁹³*See id.*

reducing gland size and differentiation, it lowers sebum production.¹⁹⁴ With less sebum in the skin, fewer pores clog and less nutrition becomes available for organisms such as *Propionibacterium acnes*, which lives in the follicle and causes the body's inflammatory response.¹⁹⁵ In addition, Accutane itself is an anti-inflammatory; it soothes pre-existing lesions to minimize scarring. In short, Accutane is a uniquely effective acne treatment.¹⁹⁶ Many patients who undergo a complete course of Accutane treatment for 15 to 20 weeks enjoy a complete and prolonged remission of the disease.¹⁹⁷

D. Accutane's Invention

Accutane was first developed in Switzerland in 1955.¹⁹⁸ At the time, its inventors recognized its teratogenicity, or ability to cause birth defects.¹⁹⁹ The drug's inventor has suggested that after the thalidomide tragedy, the use of a teratogenic drug for as seemingly benign an ailment as acne was likely to meet much opposition.²⁰⁰

E. FDA Approval of Accutane

In the late 1970s, however, Roche began testing Accutane as a treatment for severe recalcitrant acne.²⁰¹

The definition of this condition has been debated amongst doctors and regulators.²⁰² Some try to classify

¹⁹⁴ *See id.*

¹⁹⁵ *See id.*

¹⁹⁶ *See id.*

¹⁹⁷ *See House Hearings*, supra note 37, (statement of Dr. David Pariser)

¹⁹⁸ *See House Hearings*, supra note 37, (statement of Dr. James O'Donnell)

¹⁹⁹ *See Krause*, supra note 3, at 7.

²⁰⁰ *See id.*

²⁰¹ *See id.*

²⁰² Joint Meeting of the Dermatologic Drugs and the Fertility and Maternal Health Drugs Advisory Committees, (May 20,

the condition by the number and type of lesions on the patient's body.²⁰³ Others object to quantifying the classification and argue that individual doctors must diagnose the condition patient by patient rather than through a rigid general formula.²⁰⁴ Some argue that the original definition of severity has changed over time.²⁰⁵

FDA approved the drug in May 1982, making the U.S. the first country to approve Accutane as a severe recalcitrant cystic acne treatment.²⁰⁶ Roche had conducted clinical trials including 550 subject and tested the drug at four universities and the National Cancer Institute.²⁰⁷ FDA approval came nine months after the NDA submission, causing some critics to question the speed with which the drug was approved—an unusual criticism of FDA at a time when most critics considered the agency overly cautious.²⁰⁸ Widespread media coverage of the drug as a miraculous cure and relatively little media attention devoted to its risks worried some.²⁰⁹ Indeed, the drug's original package insert warned that pregnant women should not take the drug, but it explicitly stated only that Accutane caused birth defects in animals.²¹⁰

F. Education and Communication

Following Accutane's marketing, FDA and Roche made education the cornerstone of the drug's risk management program.²¹¹ One commentator Joan H. Krause, contrasts this incremental risk communication

1991), available at www.fda.gov. [hereinafter *1991 Hearings*]

²⁰³ See *1988 Hearings*, supra note 2, at 24 (statement of Dr. David Graham).

²⁰⁴ See *1991 Hearings*, supra note 201, at 134 (statement of Dr. Jerome Shupack Professor of Dermatology at New York University)

²⁰⁵ See *id.* at 184.

²⁰⁶ See Kolata, supra note 22.

²⁰⁷ See Krause, supra note 3, at 7.

²⁰⁸ See Kolata, supra note 22.

²⁰⁹ See Krause, supra note 3, at 7, 21.

²¹⁰ See *id.*, at 7.

²¹¹ See *id.* at 8-9; See also *House Hearings*, supra note 37 (statement of Dr. Jonca Bull, Deputy Director of the Office of Drug Evaluation, Center for Drug Evaluation and Research, Food and Drug Administration.)

strategy with the “sweeping changes of regulatory policy” prompted by the Thalidomide tragedy.²¹² Yet Krause’s characterization of the publicity efforts undertaken by FDA and Roche as “minor” conflicts with many commentators’ characterization of the regulatory attention devoted to the drug as unprecedented.”²¹³ Dr. Mary Spraker, in her statement at the 1991 Advisory Committee Meetings on Accutane, argues, “Never in the history of drug prescribing has more been done to educate physicians and patients about the teratogenicity of a medication.”²¹⁴ Krause herself acknowledges that FDA demonstrated laudable creativity and flexibility in the Accutane regulation and education efforts undertaken during this period.²¹⁵ Roche notified doctors of several cases Accutane related birth defects in “Dear Doctors” letters.²¹⁶ Similarly, in August 1983, FDA reported 12 cases of Accutane related “adverse pregnancy outcomes.”²¹⁷ Soon thereafter Public Citizen charged that Accutane’s warnings against pregnancy exposure were inadequate and that the drug was over-prescribed.²¹⁸ Roche soon changed Accutane’s labeling to make clear the risk of human birth defects.²¹⁹

In 1984, after reports of 21 Accutane related birth defects and 24 spontaneous abortions, Dr. Paul J. Benke identified an “isotretinoin teratogen syndrome.”²²⁰ Benke had studied two children born to Accutane users.²²¹ Based on this study, he detailed a syndrome characterized by ear, face and central nervous system problems.²²² Frequently infants exposed to the drug during pregnancy suffered from mental retardation.²²³ Benke reported that Accutane could even cause birth defects if taken by a pregnant woman only briefly during the first trimester of pregnancy, when many women are unaware of their pregnancy.²²⁴

²¹²See Krause, *supra* note 3, at 3.

²¹³See *1991 Hearings*, *supra* note 201, at 156

²¹⁴See *id.*

²¹⁵See Krause, *supra* note 3, at 21.

²¹⁶See *id.*, at 17.

²¹⁷*Id.*

²¹⁸See Philip J. Hiltz, *Acne Drug is Oversold, Group Says*, WASH. POST (Sept. 9, 1983), at A4.

²¹⁹See Krause, *supra* note 3, at 8.

²²⁰See *id.*; see also Dr. Paul J. Benke, *The Isotretinoin Teratogen Syndrome*, 251 JAMA 3267 (1984).

²²¹See Krause, *supra* note 3, at 8.

²²²See *id.*

²²³See *id.*

²²⁴See *id.*

The same year, Roche and FDA intensified warnings about Accutane's teratogenicity.²²⁵ Patients were advised to use contraception for a month before and after Accutane treatment, and blood banks were asked to reject donations from those exposed to the drug.²²⁶ Roche developed an Accutane education program targeted at physicians; in a "Medical Director's Page" printed in *the Journal of the American Medical Association*, Roche emphasized Accutane's dangers in pregnant women.²²⁷ In her testimony to the U.S. House of Representatives Committee on Government Reform, Dr. Jonca Bull, Deputy Office Director of the FDA Office of Drug Evaluation outlined the education efforts made during these years including:

1) physician labeling changes; 2) repeated mailing of special letters to doctors and pharmacists detailing proper use and emphasizing the risks; 3) two articles in FDA's Drug Bulletin, which reached more than a million health professionals, emphasizing proper prescribing of Accutane; 4) distribution to patients through doctors of a patient information leaflet highlighting the risks; 5) distribution to pharmacists of red warning stickers to be placed on each prescription bottle; and 6) issuance of press releases and background papers to the general news media for use in warning the public about the risks associated with Accutane.²²⁸

Yet by 1988 there was evidence that many women were still using the drug despite having relatively mild acne.²²⁹ The Center for Disease Control published a report of four cases of serious birth defects resulting from Accutane between 1983 and 1987.²³⁰ The CDC article also noted additional cases of birth defects.²³¹

Thus, FDA convened a Dermatologic Drugs Advisory Committee (the "Committee") meeting to address the

²²⁵ See Krause, *supra* note 3, at 8.

²²⁶ See *id.*

²²⁷ See *id.*

²²⁹ See Krause, *supra* note 3, at 9.

²³⁰ See *House Hearings*, *supra* note 37 (statement of Dr. Jonca Bull)

²³¹ See *id.*

problem.²³² Experts from several medical specialties and scientists from the CDC, FDA, Hoffman-La Roche, Public Citizen's Health Research Group, the American Academy of Pediatrics and the American Academy of Dermatology participated in day-long proceedings.²³³ In a unanimous vote, the Committee recommended the continued sale of Accutane with revised labeling and increased restrictions on the drug's distribution.²³⁴ The Committee called for new packaging featuring stronger warnings and more explicit information about Accutane's risks.²³⁵ It also recommended that the drug only be used in women who have had a negative pregnancy test.²³⁶ Finally, it recommended written acknowledgement from patients that they had been informed of Accutane's risk of birth defects.²³⁷

In a split vote, the committee also proposed the adoption of several other measures.²³⁸ Some committee members suggested that the government empower only certain types of physicians to dispense the drug.²³⁹ Others called for the imposition of special restrictions for high risk patients, including a requirement that high risk female patients obtain a second opinion.²⁴⁰ Other suggestions focused on physician awareness of Accutane's risks and proposed doctor certification for Accutane distribution through an education program.²⁴¹ Finally, the Committee recommended that the use and adverse events associated with Accutane be continually monitored.²⁴²

In May 1988, FDA issued a letter to Hoffman-La Roche discussing effective risk communication.²⁴³ While drug warnings usually appear in a package insert accompanying a drug, FDA asked that Accutane warnings appear on the blister pack containing the drug itself.²⁴⁴ These warnings included pictures depicting the

²³² See *id.*

²³³ See *id.*

²³⁴ See *id.*

²³⁵ See *id.*

²³⁶ See *id.*

²³⁷ See *id.*

²³⁸ See *id.*

²³⁹ See *id.*

²⁴⁰ See *id.*

²⁴¹ See *id.*

²⁴² See *id.*

²⁴³ See *id.*

²⁴⁴ See *id.*

severe physical abnormalities of those with Accutane-related birth defects.²⁴⁵ In addition, to facilitate the monitoring of Accutane's risks, the blister pack was to include a tear-off for mailing patient contact information to the company.²⁴⁶ FDA also called for research on patient behavior.²⁴⁷ For example, it wanted further exploration of why patients become pregnant while using Accutane.²⁴⁸ FDA then asked that both physicians and female patients signed a form acknowledging that they understood the serious likelihood that severe birth defects could result from pregnancy exposure to Accutane²⁴⁹.

FDA also focused on health care professional's education.²⁵⁰ It demanded more detailed physician and patient labeling, further educational campaigns for physicians, pharmacists as well as patients and advertisements discussing Accutane's risks.²⁵¹ Finally FDA asked that Roche run further clinical trials investigating the effectiveness of Accutane when taken at different doses for different period of time; shortening the length of Accutane therapy or the dosage of the drug could affect the risk of pregnancy exposure.²⁵²

G. Roche Pregnancy Prevention Program

By mid-1989, Roche used this risk management framework to develop a "Pregnancy Prevention Program for Women on Accutane".²⁵³ In May 1990, the Committee again evaluated the program's effectiveness and determined that the company had made a strong education effort.²⁵⁴ Nevertheless the data on its effectiveness were limited. In 1990, one case of Accutane related birth defects was reported. In 1989, there

²⁴⁵ See *id.*

²⁴⁶ See *id.*

²⁴⁷ See *id.*

²⁴⁸ See *id.*

²⁴⁹ See *id.*

²⁵⁰ See *id.*

²⁵¹ See *id.*

²⁵² See *id.*

²⁵³ See *id.*

²⁵⁴ See *id.*

were four reports and in 1988 there were three.²⁵⁵ Ten such reports were made in 1987 and twelve were made in 1986.²⁵⁶

However, the Committee made several additional recommendations. It suggested that educational materials place greater emphasis on pregnancy testing prior to the commencement of Accutane therapy.²⁵⁷ It also suggested that physicians emphasize the importance of the informed consent forms to their patients and that the forms be presented in several languages.²⁵⁸ Pregnancy prevention counseling was deemed an important component of the risk management scheme; physicians were asked to emphasize it.²⁵⁹ Finally the Committee proposed that Roche address the danger that patients will take Accutane without medical supervision by saving leftover medication.²⁶⁰ The Committee recommended that Roche arrange for the return of all leftover medication.²⁶¹

In September 2000 the Committee re-visited its discussion of fetal exposures. It decided that three principles should guide an Accutane risk management strategy on this topic.²⁶² First, no pregnant woman should begin Accutane treatment. Second, no one should become pregnant while using Accutane.²⁶³ Finally, to evaluate the program's effectiveness in meeting these goals, a monitoring program should assess results.²⁶⁴ The Committee considered the five designs FDA proposed for upholding the principles and by a majority, chose a program including education and informed consent, the registration of both patients and physicians who would fully participate in the program, the monitoring of fetal exposures using a program involving a

²⁵⁵ See *id.*

²⁵⁶ See *id.*

²⁵⁷ See *id.*

²⁵⁸ See *id.*

²⁵⁹ See *id.*

²⁶⁰ See *id.*

²⁶¹ See *id.*

²⁶² See *id.*

²⁶³ See *id.*

²⁶⁴ See *id.*

pregnancy registry, and surveys.²⁶⁵ The Committee rejected some proposals for the restricted distribution of the drug however.²⁶⁶

On October 31 2001, FDA released a Talk Paper outlining a new program designed to achieve the pregnancy prevention goals established at the September 2000 meeting.²⁶⁷ The program is called S.M.A.R.T., System to Manage Accutane Related Teratogenicity. Pursuant to its provisions, prescribers must study the S.M.A.R.T. “Guide to Best Practices,” developed by Roche and then sign and return to the company a Letter of Understanding certifying their understanding.²⁶⁸ Prescribers are also urged to take a half-day Continuing Medical Education course also developed by Roche in which specific pregnancy prevention tactics are discussed.²⁶⁹ Roche then sends to prescribers special self-adhesive Accutane Qualification Stickers.²⁷⁰ The prescriber must attach this yellow sticker to their regular prescription form to permit pharmacists to dispense the drug. Female patient’s “qualification” for Accutane entails a negative pregnancy test and education and counseling about pregnancy prevention.²⁷¹ No prescriptions are to be given for more than a one month supply so that pregnancy tests can be given monthly.²⁷²

Female patients take two urine and serum pregnancy tests prior to receiving an Accutane prescription.²⁷³ If the tests are negative they receive a prescription for a one month supply of Accutane.²⁷⁴ They must have another negative pregnancy test each month before receiving another prescription. Sexually active patients, or patients who might become sexually active with a male partner must also use two forms of effective contraception simultaneously.²⁷⁵ Contraception use must begin at least one month before the start of Accutane

²⁶⁵ See *id.*

²⁶⁶ See *id.*

²⁶⁷ Press Office, FDA, *FDA Announces Change to the Risk Management Program to Prevent Birth Defects Caused by Accutane* (2001).

²⁶⁸ See *id.*

²⁶⁹ See *id.*

²⁷⁰ See *id.*

²⁷¹ See *id.*

²⁷² See *id.*

²⁷³ See *id.*

²⁷⁴ See *id.*

²⁷⁵ See *id.*

treatment, continue throughout treatment and for at least one month after the completion of treatment.²⁷⁶ Female patients must sign a “Patients Information/Consent” form discussing Accutane’s teratogenicity.²⁷⁷ They are also asked to participate in the Accutane Survey, a confidential survey conducted by the Slone Epidemiology Unit of the Boston University School of Public Health studying S.M.A.R.T.’s effectiveness in minimizing fetal exposures.²⁷⁸

Pharmacists will only dispense Accutane if the patient presents a prescription with an Accutane Qualification Sticker.²⁷⁹ The maximum quantity pharmacists may provide is a one month supply.²⁸⁰ They will also only fill prescriptions within seven days of the “qualification” date²⁸¹ All patients will receive with the drug a Medication Guide detailing the drug’s risks, and pharmacists will refuse requests for more Accutane without a new prescription or with only a phoned-in prescription.²⁸² An independent audit of pharmacies will assess prescriber’s use of Accutane Qualification Stickers.²⁸³

H. Depression and Suicide

While controversy over Accutane related birth defects has intensified, the alleged psychiatric risks of the drug have also garnered increasing attention.²⁸⁴ Some suggest that Accutane causes depression and suicide.²⁸⁵

No reports of either problem appeared in Accutane’s original NDA safety database.²⁸⁶ Post-marketing, however, there were reports of depression in Accutane users. Again education became the center of an Accutane

²⁷⁶ See *id.*

²⁷⁷ See *id.*

²⁷⁸ See *id.*

²⁷⁹ See *id.*

²⁸⁰ See *id.*

²⁸¹ See *id.*

²⁸² See *id.*

²⁸³ See *id.*

²⁸⁴ See generally *House Hearings*, *supra* note 37.

²⁸⁵ See *id.*

²⁸⁶ See *id.*, (statement of Dr. Jonca Bull.)

risk management strategy.²⁸⁷ In the mid-1980s the drug's labeling was changed to provide, "Depression has been reported in some patients on Accutane therapy."²⁸⁸ In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstitution of therapy."²⁸⁹ The adverse reaction section of the labeling was also changed to explain, "The following CNS reactions have been reported and may bear no relation to therapy: seizures, emotional instability, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy and paresthias."²⁹⁰

In 1996, an FDA physician noted two cases of suicide in a listing of recent adverse events associated with Accutane.²⁹¹ FDA began a re-evaluation of the drug's potential link to suicide.²⁹² Dr. Bull noted that reports such as those noted in 1996 do not necessarily indicate a causal relationship between depression and Accutane use.²⁹³ Nevertheless, FDA epidemiology specialists investigated the potential link.²⁹⁴

Although these investigators did not scientifically establish a causal relationship, they did make findings suggestive of a causal link.²⁹⁵ FDA compared the number of reports to the "background rate," the rate of depression and suicide expected to be seen in the population likely to receive Accutane, teens and young adults.²⁹⁶ There were not many reports relative to the expected incidence of these problems in the teen and young adult population.²⁹⁷ Yet details of some of the reports warranted further attention. Some of the patients had apparently never experienced psychiatric symptoms prior to their Accutane treatment; there

²⁸⁷ See *id.*

²⁸⁸ See *id.*

²⁸⁹ See *id.*

²⁹⁰ See *id.*

²⁹¹ See *id.*

²⁹² See *id.*

²⁹³ See *id.*

²⁹⁴ See *id.*

²⁹⁵ See *id.*

²⁹⁶ See *id.*

²⁹⁷ See *id.*

was no other apparent reason for their symptoms.²⁹⁸ Other patients experienced depression upon beginning Accutane therapy and reported that the symptoms ended soon after the treatment ended.²⁹⁹ Some reported that the symptoms reappeared when Accutane therapy resumed.³⁰⁰

On March 3, 1997, French officials required that suicide be listed as a possible side affect of the drug.³⁰¹ FDA began working with Roche in May 1997 to address the possibility of Accutane related depression.³⁰² In February 1998, Accutane's professional label in the U.S. was again changed to explicitly highlight the risk of suicide.³⁰³ The label provided, "Psychiatric Disorders: Accutane may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events. (see Adverse reactions: Psychiatric)."³⁰⁴ The adverse reactions section listed, "psychiatric: suicidal ideation, suicide attempts, suicide, depression, psychosis (see warnings: Psychiatric Disorders), emotional instability."³⁰⁵

Doctors who might prescribe Accutane and those likely to see patients with psychiatric disturbances also received a letter about the drug.³⁰⁶ A special notice on the FDA website and a Talk Paper released to the press were also made available.³⁰⁷

Yet Roche was also running media advertisements touting Accutane's psycho-social benefits; the company implied that by treating acne the drug improves the patient's state of mind, increasing confidence and social

²⁹⁸ See *id.*

²⁹⁹ See *id.*

³⁰⁰ See *id.*

³⁰¹ Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee 154 (September 19, 2000) (statement of Liam Grant, Chairperson of the Roaccutane Litigation Group) 154 available at <http://www.fda.gov>. [hereinafter 2000 Psychiatric Hearings].

³⁰² See *House Hearings*, supra note 37, (statement of Dr.. Jonca Bull)

³⁰³ See *id.*

³⁰⁴ See *id.*

³⁰⁵ See *id.*

³⁰⁶ See *id.*

³⁰⁷ See *id.*

skills.³⁰⁸ On March 8, 1998, FDA requested that these advertisements end.³⁰⁹ FDA deemed the advertisements false and misleading.³¹⁰

The patient information regarding Accutane had included mood changes as a “sign” of potentially serious problem even before the 1998 professional labeling changes.³¹¹ Patients were advised to stop taking Accutane and to contact their doctors if they experienced mood changes.³¹² In 1998, FDA revised the patient information to provide specific information about the possible outcomes of a broader range of serious adverse events.³¹³ An interim version of this re-designed information appeared in the summer of 2000 and described the possibility that suicide can result from the mood disorders.³¹⁴ FDA critiqued this version and found that the risks were not fully described.³¹⁵ Roche agreed to explore further revisions.³¹⁶

Soon after the 1998 labeling change FDA and Roche embarked on further study of the possible connection between Accutane and psychiatric disorders.³¹⁷ Roche conducted several studies and participated in frequent working meetings with FDA.³¹⁸ Yet the studies provided no definitive evidence of a causal link between Accutane use and psychiatric disorders.³¹⁹

In October 2000 Accutane’s potential psychiatric risks received widespread attention when five-term Congressman and member of the House Committee with FDA oversight, Bart Stupak (D., Mich), and his wife Jamie appeared on *NBC-TV’s Today Show* to discuss the May 2000 suicide of their 17-year-old son B.J. Stupak.³²⁰ The teenager shot himself in the head after a post-prom party thrown for his high school friends.³²¹

³⁰⁸ See *id.*

³⁰⁹ See *id.*

³¹⁰ See *id.*

³¹¹ See *id.*

³¹² See *id.*

³¹³ See *id.*

³¹⁴ See *id.*

³¹⁵ See *id.*

³¹⁶ See *id.*

³¹⁷ See *id.*

³¹⁸ See *id.*

³¹⁹ See *id.*

³²⁰ Interview by Matt Lauer with Congressman Bart Stupak and Mrs. Jamie Stupak, NBC Today Show (Oct. 5, 2000).

³²¹ See *id.*

B.J. Stupak had undergone Accutane therapy for seven months prior to his suicide and the Stupaks accused Accutane of causing his death.³²² Congressman Stupak criticized FDA's management of Accutane risks saying:

All these people are dying, suicide thoughts, depressed, being hospitalized. The reports are coming into the FDA and they don't do anything? It takes you two and a half years to put a warning on a package. Where are they? Who's watching out? If the watchdog, the FDA, is not watching out for our children, and the consumers and the parents, who's watching out for us?³²³

Yet defenders of the drug and of FDA's risk management efforts argue that instead of being objective investigators of Accutane's risks, the Stupaks were grieving parents desperately seeking a reason for their son's death.³²⁴ Indeed some suggest that their criticism of Accutane merely deflects attention from more likely contributors to their son's suicide—their absence during his party and his access to alcohol and to a gun.³²⁵

Nevertheless, the Dermatologic and Ophthalmic Drugs Advisory Committee met again in September 2000.³²⁶ It discussed these studies of Accutane's link to depression and noted that a controlled masked clinical study was unlikely due to ethical and technical reasons.³²⁷ The Committee tried to explore other research strategies with the expert participants in the 2000 Committee hearings.³²⁸ After examining the issue of psychiatric events, the Committee agreed that the risk remained uncertain.³²⁹ Nevertheless, it considered the exploration of additional risk management strategies necessary because of the degree of concern about the drug.³³⁰ Specifically, it called for the addition of information about psychiatric adverse events to the consent form patients and physicians sign upon beginning Accutane therapy.³³¹ The Committee also recommended

³²² See *id.*

³²⁴ See *id.*

³²⁵ See Connie Giovanni, *Letters to the Editor: Acne Drugs and Suicide*, WASH POST. (Jan. 15, 2001), at A20.

³²⁶ See 2000 Hearings, *supra* note 300.

³²⁷ See *id.*

³²⁸ See *id.*

³²⁹ See *id.*

³³⁰ See *id.*

³³¹ See *id.*

that Roche provide an enhanced prescriber education program on psychiatric events and a Medication Guide for Accutane.³³² These MedGuides, patient information books, are generally only required by FDA for the few drugs that it believes pose serious risks.³³³ Further testimony on Accutane's possible association with psychiatric disorders took place before the House Committee on Government Reform in December 2000. The issue has also reached the courts. On April 11, 2002, however, one jury rejected an Oklahoma's woman's claim for \$3 million in compensatory damages for her psychiatric problems; the plaintiff, 39-year-old Carla Gray, accused Roche of negligence, but Roche's expert witnesses testified that no study demonstrates a causal link between Accutane use and depression.³³⁴

Nevertheless, another high profile law suit is now underway.³³⁵ It was brought on April 15th by Julie Bishop and Karen Johnson, the mother and grandmother respectively of 15-year old Charles Bishop, a St. Petersburg Florida teen who committed suicide by flying a stolen plane into the 28th floor of a Tampa building.³³⁶ Karen Johnson has reported that her grandson had been taking Accutane twice daily for 10 months prior to his suicide and that the drug must have made him severely psychotic.³³⁷ She and her daughter now seek \$70 million in a wrongful death action.³³⁸

Others are skeptical of Accutane's role in the suicide and even called concerns about Accutane and mental health risks "hysteria."³³⁹ One commentator views the allegations of Accutane's role in the suicide as symptomatic of society's misguided demand for definitive explanations of tragic situations. She writes, "We

³³² See *id.*

³³³ See *id.*

³³⁴ See *Daily Briefing*, ATLANTA JRNL & CONST. (Apr. 17, 2002), at 2D.

³³⁵ See Richard Jerome and Don Sider, *The Lost Boy: Grieving Mom Julie Bishop Blames and Acne Drug for her Son's Bizarre, Tragic Suicide*, PEOPLE (Apr. 29, 2002), at 107.

³³⁶ See *id.*

³³⁷ See *id.*

³³⁸ See *id.*

³³⁹ See Phillip W. DeVous, *Think Tank Wrap-up*, UNITED PRESS INTERNATIONAL, Jan 24, 2002. (arguing that no biological evidence supports the drug's link with suicide and no trace of the drug was found in Charles Bishop's bloodstream following the suicide.)

want answers. Then we want to fix whatever it is that caused the bad thing to happen. The truth is, we cannot fix everything. There are not answers to everything.”³⁴⁰

Despite its contention that no evidence suggests that Accutane causes depression, Roche has sent to more than 10,000 dermatologists a brochure concerning depression and suicide.³⁴¹ FDA approved the brochure and Roche prepared it with the help of outside experts.³⁴² The brochure informs dermatologists about the psychiatric issues most likely to be encountered in Accutane users and provides them with guidance in identifying signs of depression and other psychiatric disorders.³⁴³

Accutane’s alleged depression victims find it more difficult than those with Accutane related birth defects to prove that the drug caused their illness. Yet the alleged risk has the potential to provide an even more compelling rationale for regulation. Accutane’s teratogenicity primarily puts fertile female patients and their unborn children at risk. Psychiatric risks, by contrast, may effect both men and women, young and old

I. Patent Expiration

Roche itself has voiced new concerns about t Accutane’s risks and the importance of Accutane regulation.³⁴⁴ The last Accutane patent expired on February 7, 2002. On February 5th, Roche filed a petition with the FDA asking it not to approve generic versions of the drug until generic manufacturers instituted the rigorous safety precautions Roche has already put in place.³⁴⁵ Roche has argued that the distribution of generic

³⁴⁰Sandra Thompson, *Answers Are Elusive in Tragedy’s Aftermath*, ST. PETERSBURG TIMES, Apr. 20, 2002, at 1B

³⁴¹See Hobson, *supra* note 37.

³⁴²See *id.*

³⁴³See *id.*

³⁴⁴See Lewis Krauskopf, *Generic Accutane Faces Delays: Roche Calls for Stringent Safety Rules*, THE RECORD (Bergen County, NJ), Feb. 23, 2002, at A14.

³⁴⁵See *id.*

versions of the drug could complicate the already difficult task of tracking fetal exposures to the drug.³⁴⁶ Critics of Roche allege that the petition is merely designed to ward off competitors; generic makers of the drug are usually able to sell their product more cheaply.³⁴⁷ In the first nine months of 2001, Accutane was the company's third best-selling drug.³⁴⁸ It accounted for \$498 million in sales.³⁴⁹ Mylan Laboratories reports that it expects to win approval of its generic version this year, and generics are predicted to capture at least 20 to 25 percent of the U.S. Accutane market within a year.³⁵⁰ Although the Roche petition could delay approval of generic products, the safety concerns at stake are formidable³⁵¹ FDA is reviewing the petition and has 180 days to comment.³⁵²

IV. Regulatory Dilemmas Exemplified by Accutane Regulation

Accutane regulation and FDA's growing emphasis on post-approval controls emerge amidst fundamental regulatory dilemmas. These basic tensions, inherent in a regime that seeks to maximize both drug safety and availability, are placed into sharp relief by the Accutane experience.

A. Pre-Approval Clinical Testing:

Despite the increasing attention paid to post-approval regulation, Dr Jane Henney has emphasized, "it is

³⁴⁶ *See id.*

³⁴⁷ *See id.*

³⁴⁸ *See id.*

³⁴⁹ *See id.*

³⁵⁰ *See id.*

³⁵¹ *See id.*

³⁵² *See id.*

imperative that FDA maintain high standards in its pre-market decision-making and at the same time examine whether risks are managed throughout the healthcare delivery system.”³⁵³ Pre-market drug testing plays an important role in ensuring drug safety.³⁵⁴ Yet Accutane exemplifies the limits of even the most rigorous pre-market testing.

To best investigate drug safety, pre-clinical tests should study the drug’s effect on patients resembling those who will actually take the drug and under conditions that mirror those patients actual circumstances.³⁵⁵ Yet the people for whom the drug is intended usually have characteristics that make them particularly vulnerable to the excessive danger of a pre-approval study—illness and advanced age for example.³⁵⁶ Thus, the very patients most likely to use a drug post-marketing may be excluded from the pre-approval tests.³⁵⁷ In addition, women and racial and ethnic minorities are often underrepresented in studies, despite increasing belief that drugs may affect different races and sexes differently.³⁵⁸ Pregnant women are often excluded from clinical studies to avoid jeopardizing the health of the fetus.³⁵⁹ In their place, laboratory animals are tested.³⁶⁰ Yet sometimes even female laboratory animals are excluded because their hormonal changes complicate studies.³⁶¹

Pre-clinical testing of Accutane exemplifies this problem.³⁶² Laboratory tests showed that Accutane was teratogenic in rabbits and rats.³⁶³ Thus, women were excluded from most test centers.³⁶⁴ Elsewhere, female participants were subject to several requirements to prevent fetal exposures; they needed to have a negative pregnancy test before receiving the drug, use effective contraceptives while taking the drug and

³⁵³See Henney, *supra* note 130, at 1.

³⁵⁴See *id.*

³⁵⁵See Krause, *supra* note 3, at 10.

³⁵⁶See *id.*, at 11.

³⁵⁷See *id.*

³⁵⁸See *id.*

³⁵⁹See *id.*

³⁶⁰See *id.*

³⁶¹See *id.*

³⁶²See *id.*

³⁶³See *id.*

³⁶⁴See *id.*

agree to abort any pregnancy conceived during treatment.³⁶⁵ Because of these safeguards, no documented cases of Accutane related birth defects emerged from the tests.³⁶⁶ As a result, the drug's original labeling only reported that birth defects had occurred in laboratory animals.³⁶⁷ Some have criticized the omission of explicit reference to the risks of birth defects in humans and the failure to require that post-approval female patients comply with the same pregnancy prevention program required of female pre-approval test subjects.³⁶⁸ While Krause argues that ethical constraints often make the study of pregnant women infeasible, the Accutane experience suggests, for her, that special care should be taken to ensure that the potential risks to excluded test populations are well publicized.³⁶⁹

The Accutane experience also suggests that the most carefully designed pre-approval tests may fail to detect a drug's side effects. There were no reports of psychiatric side effects during Accutane's clinical trials.³⁷⁰ Accutane's link with depression remains uncertain and this may account for the lack of reports.³⁷¹ Reports of depression post-marketing are lower than reports of the illness in the general population.³⁷² Dr. Douglas G. Jacobs, Associate Clinical Professor of Psychiatry at Harvard Medical School and consultant to Roche, contends that there is no biochemical basis for Accutane's alleged association with psychiatric disorders.³⁷³ Yet if depression is a rare side effect of the drug, then like many rare risks, it may only appear after much larger numbers of people use the drug outside of the controlled testing environment.³⁷⁴ Some risks are so rare that they will only appear in a very small proportion of people treated with the drug.³⁷⁵ FDA's post-marketing initiatives reflect growing acceptance of the "unpalatable truth" that mass marketing is mass

³⁶⁵ See *id.*

³⁶⁶ See *id.*

³⁶⁷ See *id.*

³⁶⁸ See *id.*

³⁶⁹ See *id.*

³⁷⁰ See *House Hearings*, supra note 37 (statement of Dr. Jonca Bull)

³⁷¹ See *id.*

³⁷² See *id.*

³⁷³ See *House Hearings*, supra note 37 (statement of Dr. Douglas G. Jacobs)

³⁷⁴ See Teff, supra note 32, at 579.

³⁷⁵ See *id.*

experimentation.³⁷⁶

Pre-approval testing is particularly ill-equipped to detect psychiatric risks.³⁷⁷ At the 2000 Advisory Committee Hearings, Dr. Erick Turner reported that “when these drugs are being developed, there’s very rarely, if ever, an a priori suspicion that the drug might cause depression. So, it’s not rigorously looked for. Usually this comes up post-marketing, and they’re picked up as case reports by clinicians.”³⁷⁸

B. Off-label Usage

Charles H. Stoney Jackson, Jr., father of an Accutane patient who committed suicide has demanded, “How can a doctor prescribe a medication that is clearly licensed to be used as a treatment of last resort and for the most severe cases of acne. Clay’s [his son’s] acne was very mild, there was no reason for Clay to be using Accutane.”³⁷⁹

Once a drug is approved for marketing, individual doctors may decide how and when to prescribe that drug.³⁸⁰ Following company prescribing guidelines included in a drug’s package insert is voluntary.³⁸¹ Of course, physicians are often encouraged to comply with the guidelines by the desire use the drug safely, to provide the best service to the patient and to avoid malpractice litigation.³⁸² Yet off-label use is only indirectly constrained by these concerns.³⁸³

Off-label usage is a feature of American drug regulation intimately connected with the traditional assump-

³⁷⁶ See *id.*

³⁷⁷ See 2000 Psychiatric Hearings, *supra* note 300 (statement of Dr. Erick Turner, FDA), 101

³⁷⁸ See *id.*

³⁷⁹ See *House Hearings*, *supra* note 37 (statement of Charles H. Stoney Jackson, Jr.)

³⁸⁰ See Krause *supra* note 3, at 12.

³⁸¹ See *id.*

³⁸² See 1991 Hearings, *supra* note 201, at 156 (statement of Dr. Mary Spraker) (arguing against limitations on off-label use of Accutane.)

³⁸³ See *id.*

tions about pre-approval testing.³⁸⁴ If the FDA takes into account uses and abuses of the drug in addition to those for which the drug was originally developed, then the pre-approval trials would demonstrate the safety of most off-label uses.³⁸⁵ Indeed FDA's safety evaluation considers other probable uses or potential abuses of a drug when there is specific evidence that such use or abuse is likely to occur.³⁸⁶ However, the inherent limitations of the pre-approval process call into question the wisdom of off-label usage.³⁸⁷ Off-label usage compounds the difficulty of generalizing safety results to patient populations that differ significantly from test groups and the risk of overlooking rare or long-term side effects.³⁸⁸ The applicability of safety data to actual patient populations lessens as the drug is prescribed for conditions other than those for which the drug was intended.³⁸⁹

Nevertheless, there are significant advantages to off-label usage.³⁹⁰ Allowing off-label usage preserves physician autonomy and permits the doctors most familiar with the nuances of a patient's condition to determine that particular patient's need for a drug.³⁹¹ Strict constraints on a doctor's ability to prescribe off-label often require general practice rules that overlook the optimal treatment for the individual.³⁹² In addition, innovative uses of a drug may be discovered when physicians have the flexibility to prescribe off-label.³⁹³ It would be prohibitively expensive to test each potentially beneficial drug use from the laboratory stage forward.³⁹⁴

³⁸⁴ See Krause, *supra* note 3, at 12.

³⁸⁵ See *id.*, at 12.

³⁸⁶ See *id.*

³⁸⁷ See *id.*, at 12-13

³⁸⁸ See *id.*, at 13

³⁸⁹ See *id.*

³⁹⁰ See *id.*

³⁹¹ See 1991 *Hearings*, *supra* note 201, at 136 (testimony of Dr. Shupack)

³⁹² See *id.*

³⁹³ See Krause, *supra* note 3, at 13

³⁹⁴ See *id.*

Because doctors may prescribe Accutane off-label, they have been able to treat other skin disorders with the drug.³⁹⁵ In addition, the drug is used as a cancer treatment.³⁹⁶ Accutane contains fenretinide, a substance shown to kill cancer cells including cervical cancer and myeloid leukemia.³⁹⁷ Memorial Sloan Kettering currently uses the drug as part of its Neuroblastoma Program to combat the rare, and often fatal, childhood cancer.³⁹⁸

In stark contrast to Jackson's testimony is another father's applause of Accutane's off-label use; Scott Finestone credits Accutane with prolonging the life of his son, a neuroblastoma patient receives Accutane therapy.³⁹⁹ When administered along with bone marrow transplants, Accutane significantly improves remission in children with high risk neuroblastoma.⁴⁰⁰ Doctors have also tried, albeit unsuccessfully to date, to use Accutane to treat non-small-cell lung cancer.⁴⁰¹ Prohibiting off-label use risks stifling such creativity.⁴⁰²

Nevertheless, many critics charge that Accutane is over-prescribed for milder acne cases.⁴⁰³ As early as September 1983, Ralph Nader affiliated- Health Research Group charged that Accutane was being "overprescribed."⁴⁰⁴ The drug had been approved in 1982 to treat "severe recalcitrant acne."⁴⁰⁵ Critics have insisted that the drug was only intended for those with the most serious form of the disease; only in these cases did the drug's risks seem acceptable.⁴⁰⁶ Yet the drug was widely touted in the media as a miracle cure for acne generally.⁴⁰⁷

³⁹⁵See *1988 Hearings*, supra note 2 (testimony of Dr. Gary L. Peck) (noting that Accutane has been used to treat acne fulmanenet, meyhahans hidradentitis supparativa and keratonization disorders)

³⁹⁶See *id.*

³⁹⁷See Carolyn Susman, 'Bad' Medicine Turned Good, *PALM BEACH POST*, Apr. 4, 2002, at 1E.

³⁹⁸See *id.*

³⁹⁹See *id.*

⁴⁰⁰See *id.*

⁴⁰¹See *id.*

⁴⁰²See *id.*

⁴⁰³See Diane Knich, *Acne Drug Safeguards; Acne Drug Restrictions, Pregnancy Tests Aim to Curb Birth Defects*, *WASH. POST*, Apr. 9, 2002, at F01.

⁴⁰⁴See Hilts, supra note 217.

⁴⁰⁵See *id.*

⁴⁰⁶See *id.*

⁴⁰⁷See Krause, supra note 3, at 21.

Worries about over-prescription dominated debates at the 1988 Advisory Committee Hearings.⁴⁰⁸ Dr. David Graham, Group Leader of the Epidemiology Branch of the Office of Epidemiology and Biostatistics argued that Accutane was too frequently prescribed for mild acne cases.⁴⁰⁹ To limit off-label use, Public Citizen petitioned FDA in May 1988 to limit Accutane prescribing to board-certified or board eligible dermatologists.⁴¹⁰ Dermatologists would have had to register with FDA and receive an FDA prescriber number under this scheme.⁴¹¹ The petition demanded that Accutane prescribers certify that they had read and had promised to follow the drug's labeling and regulations.⁴¹² Public Citizen also called upon FDA to prohibit pharmacists from filling prescriptions from unregistered doctors and to subject both non-compliant doctors and pharmacists to criminal prosecution.⁴¹³

Yet dermatologists participating in the 1988 Advisory Committee hearings strongly disputed Graham's estimates and objected to the negative portrayal of the dermatologist they implied.⁴¹⁴ They regarded Graham's data and methodology as flawed and argued that most Accutane use was appropriate.⁴¹⁵ They also noted that Accutane prescriptions decreased dramatically since Accutane-related birth defects were first reported in 1983.⁴¹⁶ They also rejected Graham's claim that 85 percent of the female patients treated with Accutane had not initially been treated with antibiotics.⁴¹⁷ Instead they argued that, in the vast majority of cases, dermatologists only use Accutane after ensuring that the patient's disease is resistant to safer forms

⁴⁰⁸See generally, *1988 Hearings*, supra note 2.

⁴⁰⁹See *id.*, at 29 (statement of Dr. David Graham) (arguing that he found that excess of use in new female pat between the ages aged 15-44 could have been as high as 15-fold greater than those with the approved indication.)

⁴¹⁰See 2000 Hearings, supra note 300, at 198 (statement of Larry Sasich, Public Citizen).

⁴¹¹See *id.*

⁴¹²See *id.*

⁴¹³See *id.*

⁴¹⁴See e.g., *1988 Hearings*, supra note 2, at 110 (statement of Dr. John H. Strauss, Professor and Head, Department of Dermatology, University of Iowa) (stating, "As a dermatologist, I feel we have been indicted on the basis of evidence that can be easily challenged.")

⁴¹⁵See *id.*, at 113.

⁴¹⁶See *id.*, at 110

⁴¹⁷See *id.* at 97.

of therapy.⁴¹⁸

Yet, Dr. Lynn Silver, a pediatrician and public health expert on the staff of the Health Research Group, contended that regardless of the exact proportion of Accutane patients lacking the indicated condition, a significant amount of off-label use was occurring.⁴¹⁹ For Silver, “ Even if only one-half of the prescriptions for women was inappropriate this means that one-half of the birth defects and one-half of the abortions which occur to affected women, occurred to women who did not have a valid reason for taking this drug.”⁴²⁰ Silver’s remarks beg a fundamental question implicit in the off-label usage debate. What exactly constitutes a valid reason for taking the drug? Varying answers to the question reflect different conceptions of acne. Although doctors of all specialties share the power to prescribe Accutane, they do not share a view on the appropriate circumstances in which to use it.⁴²¹ Their disagreement reflects how notions of a disease influence its regulation.

While many dermatologists view acne as incredibly intrusive on daily life, many pediatricians suggest that these concerns pale in comparison to the devastation of birth defects.⁴²² Indeed, Dr. James L. Mills of the National Institute of Child Health and Human Development, noted that the physicians present at the 1988 hearings were split into two opposing camps; the dermatologists and the pediatricians.⁴²³

Dermatologists suggest that disfiguring acne causes as many emotional as physical scars.⁴²⁴ Dermatologists make a compelling claim that Accutane heals psychological as well as physical wounds.⁴²⁵ This notion of Accutane was put forward at the 2000 Committee hearings by Dr. Stephen Webster. One of his patients,

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⁴¹⁹ See *1988 Hearings*, supra note 2, at 146 (statement of Dr. Lynn Silver)

⁴²⁰ See *id.*

⁴²¹ See generally *1988 Hearings*, supra note 2.

⁴²² See *id.*

⁴²³ See Dr. James L. Mills, *Protecting the Embryo From X-rated Drugs*, 333 N. ENGL. JRN. OF MED. 124 (1995).

⁴²⁴ See e.g., *2000 Pregnancy Prevention Hearings*, supra note 1, at 210-211 (statement of Dr. Stephen L. Webster, former secretary-treasurer and president of the American Academy of Dermatology, a clinical professor of Dermatology at the University of Minnesota Medical School and a clinical practitioner in Wisconsin).

⁴²⁵ See *id.*

a 22-year old female college graduate with cystic acne had a marketing degree and several job interviews, but “her cystic acne is quite prominent, and in the marketing world this severely hampers her chance at a position. This acne scars more than her skin, it also scars her self-image.”⁴²⁶ Severe cystic acne had a similar effect on a 24 year old investment banker Dr. Webster treated.⁴²⁷ Dr Webster reports, “the marked facial acne cysts with a potential to scar make it difficult for him to establish his credentials. . . will people invest their money with someone with an ‘adolescent’ disease like acne.”⁴²⁸ Thus for Dr. Webster, “The effects of cystic scarring acne in any patient, but especially in young adults starting their careers, can be extensive and go beyond the skin by effecting their lives.”⁴²⁹

Similarly, Nancy Vargo, President of the Dermatology Nurses Association testified that a teenager in her family suffered from acne that “lowered his sense of self-worth and confidence and inhibited his ability to establish relationships with his peer and with others. . . Accutane. . . not only cured his acne. . . but the teenager came alive. . . he can go about the business of growing up.”⁴³⁰

Yet others counter that Accutane-exposed babies rarely have the opportunity to grow up at all.⁴³¹ They are afflicted with severely disfiguring, physically and mentally debilitating disabilities that rarely afford them the chance to live independently.⁴³² Indeed, Krause suggests that the very severity of their condition makes it easy to overlook their plight.⁴³³ While many Thalidomide victims are of normal intelligence and can tell a compelling story of the challenges their disabilities present, Accutane victims cannot voice their suffering.⁴³⁴ Indeed they may not even appear publicly in mere photographs.⁴³⁵ At the 1988 Advisory

⁴²⁶ See *id.*

⁴²⁷ See *id.*

⁴²⁸ See *id.*

⁴²⁹ See *id.*

⁴³⁰ See *id.* at 191 (statement of Nancy Varga)

⁴³¹ See 1988 *Hearings*, supra note 2, at 46 (statement of Dr Graham)

⁴³² See *id.*

⁴³³ Krause, supra note 3, at 28.

⁴³⁴ See *id.*

⁴³⁵ See 1988 *Hearings*, supra note 2 (statement of Dr. Graham).

Committee Hearings such photos were deemed so disturbing they were hidden from view.⁴³⁶ Instead, the disabilities were merely discussed verbally.⁴³⁷ Initially, Accutane patient labeling contained a photograph of a baby afflicted with Accutane-related birth defects.⁴³⁸ Later however, even this photo was replaced with a drawing, again making the victim's suffering seem less real.⁴³⁹ By contrast, acne patients can speak of their trauma and were seen repeatedly.⁴⁴⁰ Thus, care must be taken to adequately represent the plight of those exposed to Accutane during pregnancy.

This danger is far less likely to affect the alleged psychiatric victims of Accutane. The high profile suicides of B.J. Stupak and Charles Bishop are anything but invisible. At the September 2000 Advisory Committee Hearings, former Accutane patients testified to the psychiatric illnesses they had struggled with, allegedly as a result of their Accutane use.⁴⁴¹ Thirty-six year old Kimberly Smith described herself as an "Accutane survivor" after reporting that Accutane induced depression, edginess, stress and despair cost her her job and her sense of well-being.⁴⁴² Ms. Smith testified that although her skin cleared after taking Accutane, her life crumbled with the mood disorders she experienced.⁴⁴³

Debate over Accutane's appropriate use reflects concerns about physician and patient autonomy. Some scientists have taken a quantitative approach to defining severe cystic acne problem, noting, for example, definitions of 'severe' cystic acne as 10 or more deep cystic inflammatory lesions, each of 4 millimeter or more in diameter."⁴⁴⁴ The drug's labeling defines severe recalcitrant nodular acne stating, "Nodules are inflammatory lesions with a diameter of 5mm or greater."⁴⁴⁵ [Yet doctors have questioned the applicability](#)

⁴³⁶See *id.*

⁴³⁷See *id.*

⁴³⁸See Krause, *supra* note 3, at 19.

⁴³⁹See *id.*

⁴⁴⁰See 1988 Hearings, *supra* note 2.

⁴⁴¹See *e.g.* 2000 Psychiatric Hearings, *supra* note 300, at 144 (statement of Kimberley Smith)

⁴⁴²See *id.*

⁴⁴³See *id.*

⁴⁴⁴See 1988 Hearings, *supra* note 2, at 24-25 (statement of Dr. David Graham)

⁴⁴⁵Roche, Accutane Label, 6 (2002), available at <http://www.fda.gov/cder/drug/infopage/accutane/default.htm>

of these quantitative approaches to the actual practice of dermatology.⁴⁴⁶ Dr. Jerome L. Shupack opposed special post-marketing restrictions on Accutane, arguing “you cannot practice medicine by committee,” and explained:

I appreciate the efforts to quantitate [sic] what is quantifiable,[sic] but in the final analysis there are many factors which have not been looked at here, including, for one, the emotional impact of the disease, which you really cannot quantify in terms of the number of cysts or the number of pustules or what-have-you, which ends up going into the decision process...there are aspects to duration which are also quantifiable and which, again go into the decision-making progress [sic] on a day-to-day basis. For example, how much money has the patient already spent on the treatment of acne during the preceding eight to 10 years, how many drugs has he taken, how many side effects has he already had from the other drugs he has taken?⁴⁴⁷

Dr. Shupack’s remarks underscore one of the advantages of entrusting doctors with the decision to determine each patient’s individual needs. General definitions of severe acne and regulations based on uniform standards cannot capture the nuances of patient needs.⁴⁴⁸ In 1988, Dr. Gary Peck, Senior Investigator in the Dermatology Division of the NIH echoed Dr. Shupack’s concerns asking:

How many scars do you need, how many new acne cysts do you need while on conventional therapy?

How long do you have to remain on conventional therapy before you are deemed adequate to have

Accutane. I think this decision may vary with each physician.⁴⁴⁹

C. Adverse Reaction Reporting

If physicians currently have the authority to prescribe off-label, they also have the ethical responsibility to report adverse reactions to the drugs they prescribe.⁴⁵⁰ Yet the Accutane experience has highlighted weaknesses in a post-marketing surveillance programs reliant on voluntary physician reports.⁴⁵¹

⁴⁴⁶ See 1991 Hearings, supra note 201, 222, 134 (statement of Dr. Jerome L. Shupack)

⁴⁴⁸ See *id.*

⁴⁵⁰ See Krause, supra note 3, at 15.

⁴⁵¹ See *id.*

As discussed in Part II, FDA relies on an Adverse Event Reporting System (AERS) to detect adverse drug events.⁴⁵² Health care professionals and consumers voluntarily submit MedWatch forms detailing adverse events.⁴⁵³ The drug manufacturers receive approximately 94% of these forms and are required to submit them to FDA.⁴⁵⁴ These submissions must be submitted to FDA within 15 days if the event reported is serious and absent from the packages label.⁴⁵⁵ The remainder of the MedWatch forms are sent directly to FDA from the consumer or health care professional.⁴⁵⁶ MedWatch forms are the basis for individual records stored in AERS, a computer database developed in 1969 and updated in 1997.⁴⁵⁷ These records undergo computer analysis to detect patterns of adverse reactions.⁴⁵⁸

The advantages of this system lie in its simplicity.⁴⁵⁹ A small number of reported events easily signals problems to FDA and prompts further investigation.⁴⁶⁰ In addition, the system's simplicity makes it a relatively inexpensive surveillance device.⁴⁶¹ The system is also facilitates hypotheses generation regarding adverse events and provides valuable case material.⁴⁶²

Nevertheless, FDA acknowledges the system's limitations.⁴⁶³ The MedWatch forms often lack important data.⁴⁶⁴ Reporter often neglect to provide information requested of them. The forms also request descriptions of the event, but the quality of these case studies varies.⁴⁶⁵

There is also substantial, unpredictable amounts of under-reporting.⁴⁶⁶ Although manufacturers are required

⁴⁵²See Noah, supra note 35.

⁴⁵³See *id.*

⁴⁵⁴See 2000 Psychiatric Hearings, supra note 300 at 104-107 (statement of Dr. Marilyn Pitts, safety evaluator in the FDA Office of Postmarketing Research)

⁴⁵⁵See *id.*

⁴⁵⁶See *id.*

⁴⁵⁷See *id.*

⁴⁵⁸See *id.*

⁴⁵⁹See *id.*

⁴⁶⁰See *id.*

⁴⁶¹See *id.*

⁴⁶²See *id.*

⁴⁶³See *id.*

⁴⁶⁴See *id.*

⁴⁶⁵See *id.*

⁴⁶⁶See *id.*

to do so, they rely on the voluntary reports of health care workers and consumers when making these reports.⁴⁶⁷ Health care professionals and consumers may fail to report an event because they are unaware of the event or of its possible association with drug exposure.⁴⁶⁸ They may also simply avoid the burdens of reporting.⁴⁶⁹ Reporting also occurs unpredictably.⁴⁷⁰ Serious publicized events may prompt reports, a Dear Doctor letter containing warnings about a drug or publications regarding the drug in the scientific or lay media often sparks reports; events out of the public eye may go unreported⁴⁷¹

AERS reports signaled potential Accutane problems to FDA and prompted further action.⁴⁷² Accutane related pregnancy outcomes were reported to FDA by mid-1983.⁴⁷³ In response, FDA was able to increase warnings against the drug's use in pregnant women and develop education campaigns about the drug's risks.⁴⁷⁴ Similarly, reports of depression in Accutane users reached FDA via its passive post-marketing monitoring system by the mid-1980s.⁴⁷⁵ These reports prompted FDA to change the drug's labeling, educate dermatologists about psychiatric events and further investigate the potential psychiatric risks.⁴⁷⁶

Yet AERS fails to provide the data essential to scientific investigation of the reported conditions.⁴⁷⁷ An accurate assessment of the rates of pregnancy exposure to Accutane may be important in deciding how restrictive an Accutane pregnancy prevention program should be.⁴⁷⁸ In 1988, Dr. Graham argued that pregnancy-exposure to Accutane had been greatly underreported under the passive surveillance system.⁴⁷⁹

There was often an extensive lag between the occurrence of an exposure and its report to FDA.⁴⁸⁰ In the

⁴⁶⁷See *id.*

⁴⁶⁸See *id.*

⁴⁶⁹See *id.*

⁴⁷⁰See *id.*

⁴⁷¹See *id.*

⁴⁷²See Krause, *supra* note 3, at 16.

⁴⁷³See *id.*, at 7.

⁴⁷⁴See *id.*

⁴⁷⁵See *House Hearings*, *supra* note 37 (statement of Dr. Jonca Bull)

⁴⁷⁶See *id.*

⁴⁷⁷See *1988 Hearings*, *supra* note 2, at 48 (statement of Dr. David Graham)

⁴⁷⁸See *id.*

⁴⁷⁹See *id.*

⁴⁸⁰See *id.*

months leading up to the 1988 hearings, FDA received reports of exposures that had occurred more than nine months prior to the report.⁴⁸¹ Dr. Graham also reported that induced abortion after an Accutane exposure is not regularly reported to FDA.⁴⁸² Graham pointed to figures showing that 55 suspected pregnancy exposures from Michigan Medicaid and three from Group Health did not readily reach FDA's attention.⁴⁸³

Concerns about "the inertia of physician reporting in the United States" have been raised with regard to many drugs.⁴⁸⁴ In Accutane's case, the general problem of under-reporting may be exacerbated by an obstetrician's actual unawareness of a patient's Accutane use.⁴⁸⁵ Dermatologists generally prescribe Accutane; patients may fail to inform their obstetricians of an Accutane prescription.⁴⁸⁶ If the patient's child then suffers a birth defect, the obstetrician may consider the defect a product of chance.⁴⁸⁷ As a result, Graham argued, "that the tip of the iceberg has been reported to the manufacturer and FDA."⁴⁸⁸ There is a whole universe of pregnancy exposure about which we have no direct information."⁴⁸⁹

Similar problems have arisen in studying Accutane's possible psychiatric risks.⁴⁹⁰ Indeed the detection and reporting of psychiatric problems like depression may be even more difficult.⁴⁹¹ Dr. Turner reports that depression is a particularly under-recognized condition. He explains:

Symptoms are often not obvious and cannot be proven with an x-ray or lab test which may lead to some increased reluctance on the part of the person to come forward and they might dismiss it thinking, well maybe it's all just in my head. . . symptoms often get dismissed by both the person experiencing the depression, as well as perhaps family members or possibly even health care professionals.⁴⁹²

Under-reporting may be especially prevalent in adolescents, a group especially likely to suffer from acne.⁴⁹³

⁴⁸¹ See *id.*

⁴⁸² See *id.*

⁴⁸³ See *id.*

⁴⁸⁴ See *id.*

⁴⁸⁵ See *id.*

⁴⁸⁶ See *id.*

⁴⁸⁷ See *id.*

⁴⁸⁸ See *id.*

⁴⁸⁹ See *id.*

⁴⁹⁰ See 2000 Psychiatric Hearings, *supra* note 300, at 101 (statement of Dr. Erick Turner).

⁴⁹¹ See *id.*

⁴⁹³ See *id.*, at 96-97.

Adolescents often hide symptoms or have symptoms different from clinically depressed adults. Adolescent drug and alcohol problems, a common symptom of depression, are often considered a cause of the illness.⁴⁹⁴ Mood-swings are also frequently considered natural adolescent experiences rather than signs of depression.⁴⁹⁵ Further complicating the problem is the possibility that patients perceptions of acne severity itself may contribute to depression.⁴⁹⁶ People may be especially unwilling to diagnose adolescents with a potentially stigmatizing disease.

By limiting Accutane to certain prescribers and requiring patient registration, countries like Britain have monitored adverse events more closely.⁴⁹⁷ As discussed further below, the advantages of closer monitoring may be outweighed disadvantages such as reduced drug availability.

D. Accutane Education

Successful risk management is as much about communicating information as it is about gathering it. Education, rather than distribution limitations, had been the hallmark of Accutane regulation from its approval in 1983.⁴⁹⁸ As increasing numbers of birth defects were reported in the 1980s, Accutane's labeling was consistently changed to include increasingly stronger, more detailed warnings.⁴⁹⁹ Roche also advertised the drug's risk's in medical and pharmacy journals.⁵⁰⁰ In May 1984, FDA's Dermatologic Drugs Advisory Committee rejected restrictions on the drug's availability and favored further warnings to ensure proper use and mini-

⁴⁹⁴ See *id.*

⁴⁹⁵ See *id.*

⁴⁹⁶ See *id.*

⁴⁹⁷ See Kolata, *supra* note 22

⁴⁹⁸ See Krause, *supra* note 2, at 17-20.

⁴⁹⁹ See *id.*

⁵⁰⁰ See *id.*

mize its risks.⁵⁰¹ These publicity efforts continued until the 1988 Advisory Committee suggested unusually strict limits on the drug's use.⁵⁰² Yet FDA was reluctant to limit access to the drug. Instead it required risk communication measures such as revised patient labeling.⁵⁰³ On September 19, 1988, unique "Pregnancy Prevention Kits" were distributed.⁵⁰⁴ Labels then depicted children with typical Accutane related deformities, a "non-pregnancy symbol" on every page.⁵⁰⁵ Revised physician labeling advised against prescribing the drug to patients who failed to understand its risks and that patients have a negative pregnancy test within 2 weeks of beginning treatment.⁵⁰⁶ Also developed were a detailed informed consent form, a revised patient brochure also featuring the Accutane victim depiction, and blister packaging with non-pregnancy symbols on the packaging of each dose and tear-off post-cards for patients to provide information about informed consent.⁵⁰⁷ By October 1989, Roche had launched an unusual advertising campaign directed at dermatologists and stressing Accutane's risks rather than its benefits.⁵⁰⁸ By 1991, the company had also developed an Accutane videocassette for patients to view in the doctor's office.⁵⁰⁹

Yet critics such as Public Citizen have regarded education and publicity as a the mere "Pavlovian response to drug safety issues by manufacturers and the FDA."⁵¹⁰ Public Citizen's suggestion that warnings have been a mere automatic reaction to Accutane risks overlooks the thoughtful care and preparation devoted to Accutane education campaigns.⁵¹¹ Nevertheless, commentators have raised legitimate concern about the

⁵⁰¹ See *id.*, at 18.

⁵⁰² See *id.*

⁵⁰³ See *id.*

⁵⁰⁴ See *id.* at 19.

⁵⁰⁵ See *id.*

⁵⁰⁶ See *id.*

⁵⁰⁷ See *id.*

⁵⁰⁸ See *id.*

⁵⁰⁹ See *id.* at 20.

⁵¹⁰ See 1988 Hearings *supra* note 2, at 201 (statement of Larry Sasich)

⁵¹¹ See *id.*

efficacy of the Accutane warnings.⁵¹²

Krause lauded FDA for the creativity of its post-marketing Accutane education efforts, but criticized the initially lax warnings accompanying the drug; the drug's failure to clearly indicate that it could cause birth defects in human patients was troubling.⁵¹³ In addition, Krause noted that literature based warnings written only in English might have made it more difficult for the illiterate and non-English speakers to access information.⁵¹⁴

Perhaps the most formidable obstacle to successful warnings were mass media reports of the drug's benefits. The portrayal of Accutane as a "miracle cure" probably increased consumer demand. By contrast, physicians, rather than consumers, were the primary audience for many of the Accutane education efforts. While Roche engaged in a risk education campaign, it also ran advertisements touting the drug's psychological benefits.⁵¹⁵ Krause suggests that more intense mass media campaigns should have publicized Accutane's dangers.

At the 2000 Advisory Committee meeting, Dr. Peter Honig of FDA's Office of Postmarketing Drug Risk Assessment expressed FDA's waning confidence even in doctor-targeted warnings.⁵¹⁶ Citing experiences with other drugs such as Seldane, Dr. Honig argued that labeling changes and passive educational campaigns have traditionally done relatively little to manage risk.⁵¹⁷ He concluded, "I think it is clear that labeling changes and Dear Doctor letters are relatively ineffective ways of communicating risk if your intention is changing behavior."⁵¹⁸

Dr. Honig detailed obstacles to translating education into action.⁵¹⁹ His study points to labeling fatigue—

⁵¹²See *id.*

⁵¹³See Krause, *supra* note 3, at 21.

⁵¹⁴See *id.*

⁵¹⁵See *House Hearings*, *supra* note 37, (statement of Dr. Jonca Bull).

⁵¹⁶See 2000 Hearings, *supra* note 1, at 31 (statement of Dr. Peter Honig).

⁵¹⁷See *id.*

⁵¹⁸*Id.*

⁵¹⁹See *id.*

the difficulty of changing behavior with numerous labeling revisions if the initial revisions are ineffective.⁵²⁰ Information overload and the law of diminishing returns works against behavior change in these cases.⁵²¹ Citing research on clinical practice guidelines, Dr. Honig discussed factors limiting physicians' adherence to clinical practice guidelines.⁵²² Unawareness of the guidelines, lack of familiarity with them, disagreement with them and doubt that adherence will produce results can be major impediments to adherence.⁵²³ In addition, "the inertia of previous practice" can contribute to the problem; as recommendations change frequently adherents to the most recent advice dwindle.⁵²⁴ Finally, there are "external barriers" of inconvenience and confusion.⁵²⁵ These external barriers may only worsen as managed care systems proliferate.⁵²⁶ Shorter patient visits and patient-doctor relationships hinder education efforts.⁵²⁷ Pregnancy prevention and psychiatric illness alike implicate sensitive personal issues difficult to discuss with strangers.⁵²⁸ Frequent doctor changes and briefer visits are not conducive to such education efforts.⁵²⁹

Thus, as problems with effective education become apparent, emphasis on post-approval restrictions look more appealing.

E. Post-Approval Controls

⁵²⁰ *See id.*

⁵²¹ *See id.*

⁵²² *See id.*

⁵²³ *See id.*

⁵²⁴ *See id.*

⁵²⁵ *See id.* at 35.

⁵²⁶ *See* Noah, *supra* note 35, at

⁵²⁷ *See id.*

⁵²⁸ *See id.*

⁵²⁹ *See id.*

Post-approval controls may minimize the occurrence of adverse events. Yet these safety controls may also carry the price of limited drug access.⁵³⁰ Indeed by making it more difficult to obtain a drug, post-approval controls may foster an unregulated underground market for the drug featuring little, if any, safety precautions for drug users.⁵³¹ Safety controls can also intrude on the autonomy and privacy of the patients themselves, conditioning prescriptions on invasive requirements. The Accutane experience illustrates all of these concerns.

Some have proposed that Accutane should only be distributed from regional centers.⁵³² Such a program would mirror the British model of Accutane regulation under which Accutane may only be prescribed by a select group of dermatologists.⁵³³ Patients are referred to one of these specialists by their own doctors and must be warned of the risks of pregnancy, given a written warning, required to sign a consent form and to agree to an immediate abortion if they become pregnant while taking the drug.⁵³⁴

Dr. Mary Spraker objected to this proposal citing concerns about inconvenience to the patient, increased cost and a questionable reduction of actual pregnancy exposures.⁵³⁵ This “regional center” concept may make it far more difficult for patients outside of major cities to obtain the drug.⁵³⁶ Patients from rural areas may have to travel miles for care.⁵³⁷ Even city residents could find it difficult to find a registered pharmacy.⁵³⁸ The program imposes both physical and psychological barriers to Accutane use.⁵³⁹ By forcing a patient to switch from an unregistered to an registered doctor, we disrupt a crucial doctor-patient relationship in

⁵³⁰See *1991 Hearings*, supra note 201, at 157 (statement of Dr. Mary Stupak)

⁵³¹See *id.*

⁵³²See *id.*

⁵³³See Kolata, supra note 22.

⁵³⁴See *id.*

⁵³⁵See *1991 Hearings*, supra note 201, at 157 (statement of Dr. Mary Spraker)

⁵³⁶See *id.*

⁵³⁷See *2000 Pregnancy Prevention Hearings*, supra note 1, at 178 (statement of Dr. Barbara Reed, dermatologist, American Academy of Dermatology.)

⁵³⁸See *id.*

⁵³⁹See *id.*

which the evaluation of a patient's reliability and the necessity of discussing sensitive pregnancy prevention issues are paramount concerns. Financial barriers may also rise.⁵⁴⁰ Dr. Spraker further argues that such a regulatory system would increase the cost of the already expensive Accutane.⁵⁴¹ The tightly monitored anti-psychotic drug Clozapine has effectively been rationed by the price increases under its mandatory monitoring system.⁵⁴²

In addition, Dr. Spraker questioned the ultimate efficacy of a "center use" approach.⁵⁴³ She noted that despite receiving pregnancy counseling and receiving the drug from a limited center patients can still become pregnant while using the drug.⁵⁴⁴ Dr. Barbara Reed likened conception while on Accutane to other risk-taking behaviors such as reckless driving and doubted that any amount of monitoring and education could "legislate pregnancy prevention."⁵⁴⁵

Indeed, such a regulatory regime might spur unauthorized use of the drug, a phenomenon likely to produce more, not less, pregnancy exposures.⁵⁴⁶ The regime might pressure people to engage in drug sharing.⁵⁴⁷ Alternatively, those unable to obtain the drug legally may look to underground markets.⁵⁴⁸ Recently, Accutane was found among several prescription drugs seized in a raid of Contra Costa, California supermarkets.⁵⁴⁹ The drugs, which appear to have been manufactured in Mexico, were sold over-the-counter to anyone with the ability to pay.⁵⁵⁰ California officials suspect that the practice is widespread.⁵⁵¹

The Internet may only exacerbate this problem. The Roaccutane Action Group has alleged that it has

⁵⁴⁰See *id.*

⁵⁴¹See *1991 Hearings*, supra note 201, at 157.

⁵⁴²See *id.*

⁵⁴³See *id.*

⁵⁴⁴See *id.*

⁵⁴⁵See *2000 Pregnancy Prevention Hearings*, supra note 1, at 179.

⁵⁴⁶See *id.*

⁵⁴⁷See *id.*

⁵⁴⁸See *id.*

⁵⁴⁹See Kate Darby Rauch, *Contra Costa County Seizes Hundreds of Illegal Pharmaceuticals in Raid*, CONTRA COSTA TIMES, Apr. 19, 2002.

⁵⁵⁰See *id.*

⁵⁵¹See *id.*

already obtained Accutane by placing an online order for the drug under the names of teenagers.⁵⁵² It received the drug from South Africa within only 10 days of the request, accompanied by a prescription from a doctor with a South African address.⁵⁵³ The Group paints a frightening portrait of Internet drug marketing explaining, “all you need is a credit card. No medical consultation. No meeting between patient and doctor. No blood tests. No birth control safeguards. No monitoring of patients.”⁵⁵⁴

F. Patient Autonomy

While concern about the underground drug market centers on its extreme lack of government regulation, critics of post-marketing regulation worry about excessive government intrusions. Just as dermatologists have called for physician autonomy, many participants in the Accutane debate have called for patients’ autonomy, particularly female patient’s autonomy.⁵⁵⁵

Concerns about fetal exposure are well justified. A fetus exposed to Accutane only 15 days after fertilization may suffer from birth defects and many women are unaware of their pregnancies at this point. Effectively monitoring pregnancy status is thus particularly important during Accutane therapy. Indeed, some have asked if a self-pregnancy test could accompany each daily dose of the drug to facilitate monitoring.⁵⁵⁶ (252).

In a similar vein, some have suggested that patients be required to prove that they use several forms of contraception.⁵⁵⁷ Others advocate the mandatory use of injectable contraceptives.⁵⁵⁸

⁵⁵² See 2000 Hearings, supra note 1, 147 (statement of Liam Grant) (Roaccutane is the trade name of Isotretinoin in Britain.)

⁵⁵³ See *id.* at 157.

⁵⁵⁴ See *id.*

⁵⁵⁵ See Krause, supra note 3, at 28.

⁵⁵⁶ See 2000 Pregnancy Prevention Hearings, supra note 1, 252.

⁵⁵⁷ See 2000 Pregnancy Prevention Hearings, supra note 1, at 289 (statement of Dr. Michael Greene, Department of Obstetrics and Gynecology, Mass General Hospital).

⁵⁵⁸ See *id.*

Among the most passionate advocates of pregnancy prevention measures are thalidomide victims.⁵⁵⁹ The Thalidomide Victims Association of Canada testified at the 2000 Advisory Committee hearings in support of pregnancy prevention measures.⁵⁶⁰ The group was formed in 1988 to support and empower Canadian “thalidomiders”.⁵⁶¹ In 1995, the Association became involved in the thalidomide licensing issue; it demanded the implementation of a mandatory compliance program to minimize pregnancy exposures to thalidomide used in women with severe illnesses.⁵⁶² Thalidomide was licensed under the restrictive STEPS program which requires a mandatory physician, patient and pharmacy registry.⁵⁶³ Only those registered may prescribe, dispense or use the drug. Registry is prohibitively expensive and few if any doctors in private practice can afford those cost. In addition, relatively few patients have been registered.⁵⁶⁴

Since then the Thalidomide group has become involved in debates over the management of many teratogenic drugs.⁵⁶⁵ It is determined “to remind those making these decisions [as to the risks and benefits of Accutane] that the risks can always be lessened by responsible thinking... If mandatory compliance lessens pain for just one family, creating one less victim, it is worth it. No amount of compensation can amount to a healthy body.”⁵⁶⁶

Accutane’s use in teenagers makes the risk of pregnancy exposure more troubling.⁵⁶⁷ Teenagers often fail to report their sexual activity and are especially unlikely to use birth control.⁵⁶⁸ As Dr. Amarilyas Vega noted, “We know that sexual activity status from not being sexually active to becoming sexually active

⁵⁵⁹See 2000 Pregnancy Prevention Hearing, *supra* note 1, at 206 (statement of Randall Warren, CEO of the Thalidomide Victims Association.)

⁵⁶⁰See *id.*

⁵⁶¹See *id.*

⁵⁶²See *id.*

⁵⁶³See *id.*

⁵⁶⁴See *House Hearings*, *supra* note 37. (statement of Dr. Pariser)

⁵⁶⁵See 2000 Pregnancy Prevention Hearing, *supra* note 1, at 206 (statement of Randall Warren, CEO of the Thalidomide Victims Association.)

⁵⁶⁶See *id.*, at 209.

⁵⁶⁷See *1988 Hearings*, *supra* note 2, at 148 (statement of Dr. Lynn Silver)

⁵⁶⁸See *1988 Hearings*, *supra* note 2. (statement of Dr. Nancy Lee, Division of Reproductive Health, CDC)

may change overnight.”⁵⁶⁹ This is particularly true for adolescents.⁵⁷⁰ They often report that they fail to use birth control because they do not expect to have intercourse.⁵⁷¹ Despite reporting abstinence to their dermatologists, they may unwittingly expose their unborn child to Accutane.⁵⁷² As the Thalidomide Victims Association reminds, the consequences of such exposures could be devastating.⁵⁷³

However, the competing interest in patient autonomy counsels against restrictive drug regulatory regimes. Dr. Michael Greene expressed alarm at some of the pregnancy prevention programs contemplated by fellow participants in the 2000 hearings.⁵⁷⁴ For him, many of these schemes would intrude too deeply on women’s autonomy.⁵⁷⁵ He explained:

If a woman is fully informed – I’m not talking about a child or a minor, but if a fully informed woman says that she is abstinent and says that, recognizing everything that we’ve had to say about the risks associated with taking Accutane that she doesn’t need and doesn’t want contraception, I would have a tough time telling that adult woman that she can’t make that decision for herself, as an obstetrician/gynecologist. So I view with a little bit of alarm some of what I consider to be rather draconian proposals that would ride roughshod over an adult, competent woman’s autonomy.⁵⁷⁶

Dr. Barbara Reed, a dermatologist who initially spent 12 years practicing gynecology, opposed mandatory registration of Accutane patients for similar reasons.⁵⁷⁷ She suggests the dangers of a slippery slope that would increasingly limit women’s freedom in the name of the unborn.⁵⁷⁸ For her, Accutane use implicates the same issues involved in fetal alcohol syndrome and other diseases related to a pregnant women’s risky behavior.⁵⁷⁹ Reed asks, “Are we going to have a registry for buyers and sellers of non-steroidal anti-inflammatory drugs and alcohol. Cigarettes is another one.”⁵⁸⁰

⁵⁶⁹See *2000 Pregnancy Prevention* hearings, supra note 1, 51 (statement of Dr. Amarlyas Vega)

⁵⁷⁰See *id.*

⁵⁷¹See *id.*

⁵⁷²See *id.*

⁵⁷³See *2000 Pregnancy Prevention Hearings*, supra note 1, at 206 (statement of Randall Warren).

⁵⁷⁴See *2000 Pregnancy Prevention Hearings*, supra note 1, (statement of Dr. Michael Greene)

⁵⁷⁵See *id.*

⁵⁷⁷See *id.*, at 179 (statement of Dr. Barbara Reed)

⁵⁷⁸See *id.*

⁵⁷⁹See *id.*

⁵⁸⁰See *id.*

These concerns are not new. At the 1991 Advisory Committee hearings, Dr. Mary Spraker, a practicing academic pediatric dermatologist, rejected proposals that every patient take an oral, injectable or implantable contraceptive, despite the patient's commitment to abstinence or the continued use of her current contraception device.⁵⁸¹ Dr. Spraker insisted that the patient should possess the ultimate power to make contraceptive decisions; she argued that doctors should respect a patient's unwillingness to undertake the risks of contraceptive use, to experience invasive device placement procedures or to incur the expense of implantable contraceptives.⁵⁸² She argued, "The patients, once given the alternatives with the prospective pros and cons, has the right to participate in the choice of her own contraceptive."⁵⁸³ We need to recognize that as physicians we can guide our patients, but we do not have, and do not want, the power to control them."⁵⁸⁴

Perhaps most invasive are requirements found in some European countries, such as Britain, mandating that female Accutane patients agree to abort any pregnancy that occurs while taking the drug.⁵⁸⁵ Such a proposal in U.S. drug regulation would directly engage the controversial abortion issue. Roche's pregnancy counseling program includes discussion of emergency contraception and the 'morning-after pill,' and at least some commentators have argued that Roche should pay for the therapeutic abortions often elected by women whose children have been exposed to the drug.⁵⁸⁶

G. System to Manage Accutane Related Teratogenicity (S.M.A.R.T.)

FDA announced its new S.M.A.R.T program amidst this debate.⁵⁸⁷ The program reflects FDA's growing

⁵⁸¹See 1991 Hearings, *supra* note 201, at 158 (statement of Dr. Mary Spraker.)

⁵⁸²See *id.*

⁵⁸³See *id.*

⁵⁸⁴See *id.*

⁵⁸⁵See Kolata, *supra* note 22.

⁵⁸⁶See *2000 Pregnancy Prevention Hearings*, *supra* note 1, at 223.

⁵⁸⁷See FDA Press Office, *supra* note 266, at 1

commitment to more active post-marketing regulation. Yet it also illustrates continued respect for both patient and doctor autonomy. While S.M.A.R.T. includes unusually restrictive post-approval drug regulation, it does not go as far in monitoring and limiting Accutane use as many advocates for Accutane controls would have liked.⁵⁸⁸ Indeed S.M.A.R.T. is not as dramatic a departure from the traditional focus of Accutane regulation on warnings and education, rather than distribution limitations.

S.M.A.R.T. exemplifies the kind of active post-marketing regulation contemplated by the Task Force. Rather than merely recommending that doctors test female patients for pregnancy, the program requires that two pregnancy tests be performed both prior to commencing therapy and each month thereafter throughout the course of the therapy.⁵⁸⁹ Prescribers sign a “Letter of Understanding” promising to perform these tests. The program similarly requires the choice of two forms of birth control, unless absolute abstinence will be practiced during therapy and for one month after its completion, or the patient has had a hysterectomy.⁵⁹⁰ Placement of the Accutane Qualification sticker on the doctor’s prescription form certifies compliance with the safeguards.⁵⁹¹ These measures are unusually specific and mandatory. In addition, signing and returning the form essentially registers the doctor to prescribe the drug.⁵⁹² In addition patients are required to sign and return an informed consent form which effectively registers them as well.⁵⁹³

Also unusual is S.M.A.R.T.’s prohibition of pharmacy distribution of Accutane to those without an Accutane Qualification sticker.⁵⁹⁴ Roche had questioned the wisdom of placing pharmacists in an essentially regulatory role with regard to doctors and argued that such a role extends beyond pharmacy practice guide-

⁵⁸⁸ See Knich, *supra* note 402.

⁵⁸⁹ See FDA Press Office, *supra* note 266, at 1.

⁵⁹⁰ See *id.*

⁵⁹¹ See *id.*

⁵⁹² See *id.*

⁵⁹³ See *id.*

⁵⁹⁴ See *id.*

lines by intruding too extensively on the practice of medicine.⁵⁹⁵ Yet S.M.A.R.T. forbids pharmacists from filling prescriptions lacking the sticker.⁵⁹⁶ It also requires them to fill prescriptions within seven days of the prescription's date and to distribute a large medication guide with the drug.⁵⁹⁷ One pharmacist has called the measures "extraordinary. . . almost a matter of overkill."⁵⁹⁸

These limitations fall squarely within the post-approval controls suggested by the Task Force on Risk Management.⁵⁹⁹ The Report explicitly suggested the imposition of safety programs for risky products.⁶⁰⁰ It noted increasing acceptance by the medical profession's acceptance of post-marketing regulation of such programs.⁶⁰¹ Press reports on S.M.A.R.T. label it "unusually strict" and note its departure from traditional reliance solely on medical professionals to informally implement pregnancy prevention standards.⁶⁰²

Nevertheless, Public Citizen argues that S.M.A.R.T. is not enough of a departure from tradition.⁶⁰³ Dr. Sidney Wolf continues to call for limitation of Accutane prescribing to select specialists. He remains concerned about possible over-prescription of the drug and views the limitation on prescribers as the best means of combating the problem.⁶⁰⁴ S.M.A.R.T., however, is more protective of preserving access to the drug. It is also more protective of women's autonomy than other proposals for more restrictive regimes. Unlike proposals ventured at Advisory Committee Hearings, the program also permits those who promise to practice absolute abstinence to forgo birth control while taking the drug.⁶⁰⁵ In addition, the Continuing Medical Education course that Roche has developed for physicians remains optional.⁶⁰⁶ The program certainly does not mandate the termination of pregnancies conceived during therapy.⁶⁰⁷

⁵⁹⁵ See *2000 Pregnancy Prevention Hearings*, supra note 1, at 153.

⁵⁹⁶ See FDA Press Office, supra note 266, at 2.

⁵⁹⁷ See Knich, supra note 402.

⁵⁹⁸ See *id.*

⁵⁹⁹ See Report, supra note 41, at 92-94

⁶⁰⁰ See *id.*

⁶⁰¹ See *id.*, at 92.

⁶⁰² See Knich, supra note 402.

⁶⁰³ See *id.*

⁶⁰⁴ See *id.*

⁶⁰⁵ See *id.*

⁶⁰⁶ See FDA Press Office, supra note 266, at 2.

⁶⁰⁷ See *id.*

Although the program is easily categorized as a form of “risk intervention” in the language of the Task Force’s Report, its primary means of effecting change may occur through its risk communication aspects. The required consent forms, and Letters of Understanding and Medication Guides contain substantive information on risks.⁶⁰⁸ Yet, in themselves, the very hurdles doctors and patients must clear in order to obtain the drug signals the perceived importance of the risks at stake. Regardless of the content of the warnings, these obstacles alone communicate FDA’s concerns about pregnancy prevention. Thus it may have a cautionary effect on both prescribers contemplating the appropriateness of Accutane therapy for their patients and on patients engaging in a pregnancy prevention strategy. The program mandates certain behavior—the frequent pregnancy tests and use of birth control in sexually active women—but it has a large educational component as well.⁶⁰⁹ Thus it follows in the tradition of the risk communication emphasis in Accutane regulation.

Yet according to Jonathan Wilkin, director of FDA’s Division of Dermatologic and Dental Drug Products Division, FDA is prepared to impose even stricter regulation if S.M.A.R.T. fails to reduce Accutane –related birth defects.⁶¹⁰ Thus S.M.A.R.T. may be just the beginning both of Accutane’s post-marketing controls and of post-marketing regulation more broadly in American drug policy making.

V. Conclusion

Accutane exemplifies the central conflict in drug regulation between ensuring drug safety and maximizing drug availability. The Accutane experience reflects a growing trend towards recognizing the need for stronger post-marketing drug regulation in striking the correct balance between these goals. S.M.A.R.T. takes a

⁶⁰⁸ See *id.*

⁶⁰⁹ See *id.*

⁶¹⁰ See Knich, *supra* note 402.

dramatic step towards implementing the risk management suggestions of the Task Force on Risk Management in the fight to protect patients from Accutane's teratogenic risks and alleged psychiatric consequences. Yet, perhaps wisely, it does not impose as intrusive a regulatory regime as possible thereby preserving as much patient and physician independence as possible in combating a potentially serious illness.